FA

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40456 A1

(51) International Patent Classification[7]: C07D 241/18, 241/20, 405/12, 213/82, 213/60, 213/64, 213/74, A61K 031/497, 31/445, 31/4427, A61P 25/00, 25/18, 13/00, 25/04

(21) International Application Number: PCT/SE01/02569

(22) International Filing Date:
20 November 2001 (20.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0004245-7	20 November 2000 (20.11.2000)	SE
60/253,509	28 November 2000 (28.11.2000)	US

(71) Applicant *(for all designated States except US)*: **BIOVITRUM AB** [SE/SE]; S-112 76 Stokholm (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **NILSSON, Björn** [SE/SE]; Djäknegatan 15:650, S-754 23 Uppsala (SE).

(74) Agent: **HÖGLUND, Lars**; Biovitrum AB, S-112 76 Stockholm (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/40456 A1

(54) Title: PIPERAZINYLPYRAZINE COMPOUNDS AS AGONIST OR ANTAGONIST OF SEROTONIN 5HT-2 RECEPTOR

(57) Abstract: A compound of the general formula (I), wherein R_1, R_2, X, Y and Z are as described in the specification.

PIPERAZINYLPYRAZINE COMPOUNDS AS A AGONIST OR ANTAGONIST OF SEROTONIN 5HT-2 RECEPTOR.

Field of the Invention

The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament which particularly acts on the central nervous system.

Background of the Invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic, and the serotonergic neurotransmitter systems. For example, serotonin has been implicated in a number of diseases and conditions which originate in the central nervous system. A number of pharmacological and genetic experiments involving receptors for serotonin strongly implicate the 5-HT_{2c} receptor subtype in the regulation of food intake (Obes. Res. 1995, 3, Suppl. 4, 449S-462S). The 5-HT_{2c} receptor subtype is transcribed and expressed in hypothalamic structures associated with appetite regulation. It has been demonstrated that the 5-HT_{2c} receptor agonist *m*-chlorophenylpiperazine (mCPP), which has some preference for the 5-HT_{2c} receptor, reduces food intake in mice that express the normal 5-HT_{2c} receptor while the compound lacks activity in mice expressing the mutated inactive form of the 5-HT_{2c} receptor (Nature 1995, 374, 542-546). In a recent clinical study, a slight but sustained reduction in body weight was obtained after 2 weeks of treatment with mCPP in obese subjects (Psychopharmacology 1997, 133, 309-312). Recently, a series of pyrrolo[3,2,1-*ij*]quinoline derivatives was identified to be 5-HT_{2C} receptor agonists having selectivity over the 5-HT_{2A} receptor (Isaac M., et al., Bioorg. Med. Chem. Lett. 2000, 10, 919-921). The compounds are said to offer a novel approach to the treatment of obesity and epilepsy.

Weight reduction has also been reported from clinical studies with other "serotonergic" agents (see e.g. IDrugs 1998, 1, 456-470). For example, the 5-HT reuptake inhibitor fluoxetine and the 5-HT releasing agent/reuptake inhibitor dexfenfluramine have exhibited weight reduction in controlled studies. However,

currently available drugs that increase serotonergic transmission appear to have only a moderate and, in some cases, transient effects on the body weight.

The 5-HT_{2c} receptor subtype has also been suggested to be involved in CNS disorders such as depression and anxiety (Exp. Opin. Invest. Drugs 1998, 7, 1587-1599; IDrugs, 1999, 2, 109-120).

The 5-HT_{2c} receptor subtype has further been suggested to be involved in urinary disorders such as urinary incontinence (IDrugs, 1999, 2, 109-120).

Compounds which have a selective effect on the 5-HT_{2c} receptor may therefore have a therapeutic potential in the treatment of disorders like those mentioned above. Of course, selectivity also reduces the potential for adverse effects mediated by other serotonin receptors.

Information Disclosure

US-A-3,253,989 discloses the use of mCPP as an anorectic agent.

EP-A1-863 136 discloses azetidine and pyrrolidine derivatives which are selective 5-HT_{2c} receptor agonists having antidepressant activity and which can be used for treating or preventing serotonin-related diseases, including eating disorders and anxiety.

EP-A1-330 263 discloses piperazinylalkylpyrimidines as hypoglycemic agents.

WO 87/04928 discloses 2-(1-piperazinyl)pyrimidines as agents for treating neuropathy.

EP-A2-226842 discloses 1,4-naphthalenedione heterocyclic derivatives as antiallergics and antiasthmatics including 2-(3-bromophenyl)-4-(1-piperazinyl)-pyrimidine.

EP-A-657 426 discloses tricyclic pyrrole derivatives having activity on the 5-HT_{2c} receptor and which inter alia may be used for treating eating disorders.

EP-A-655 440 discloses 1-aminoethylindoles having activity on the 5-HT_{2c} receptor and which may be used for treating eating disorders.

EP-A-572 863 discloses pyrazinoindoles having activity on the 5-HT_{2c} receptor and which may be used for treating eating disorders.

J. Med. Chem. 1978, 21, 536-542 and US-A-4,081,542 disclose a series of piperazinylpyrazines having central serotonin-mimetic activity.

US 4,078,063 discloses a series of piperazinylpyridines having anorexic activity.

J. Med. Chem. 1981, 24, 93-101 discloses a series of piperazinylquinoxalines with central serotoninmimetic activity.

ES 514549 discloses piperazine derivative with anorexigenic action.

EP 370560 discloses 1-[mono- or bis(trifluoromethyl)-2-pyridinyl]piperazines as central nervous system agents.

J. Med. Chem. 1987, 30, 1794-1798 discloses 2-(4-heterocyclylpiperazin-1-yl) derivatives including 2-phenoxy-4-piperazin-1-ylpyrimidine.

DE 2202385 discloses antimicrobial (5-nitro-2-furyl)pyrimidines and –thiadiazoles including 2-(5-nitro-2-furyl)-4-(4-methyl-1-piperazinyl)pyrimidine and 2-(5-nitro-2-furyl)-4-[4-(2-hydroxyethyl)-1-piperazinyl]pyrimidine.

J. Med Chem. 1987, 30, 1210-1214 discloses *N,N*-disubstituted 6-alkoxy-2-pyridinamines as anticonvulsant agents including 1-(6-methoxy-2-pyridinyl)piperazine, 1-(6-ethoxy-2-pyridinyl)piperazine, 1-(6-isopropoxy-2-pyridinyl)piperazine, 1-(6-isobutoxy-2-pyridinyl)piperazine, 1-(6-cyclopropylmethoxy-2-pyridinyl)piperazine, 1-(6-cyclohexylmethoxy-2-pyridinyl)piperazine, and 1-(6-cyclohexyloxy-2-pyridinyl)piperazine.

J. Med. Chem. 1989, 32, 1237-1242 discloses 6-alkyl-*N,N*-disubstituted-2-pyridinamines as anticonvulsant agents including 1-(6-butylthio-2-pyridinyl)piperazine, 1-(6-cyclohexylmethyl-2-pyridinyl)piperazine and 1-[6-(2-phenylethyl)-2-pyridinyl]piperazine.

JP 07300474 discloses drugs for treatment of diseases related to serotoninergic nerve including 1-(6-phenoxy-2-pyridinyl)piperazine and 1-[6-(substituted)phenoxy-2-pyridinyl]piperazines, 1-(6-benzyloxy-2-pyridinyl)piperazine, 1-(6-cyclobutyloxy-2-pyridinyl)piperazine, and 1-(6-cyclopentyloxy-2-pyridinyl)piperazine

EP 580465 discloses heterocyclic piperazines as 5-HT_3 agonists including

6-chloro-2-(3-methylpiperazinyl)pyridine and 6-chloro-2-(4-methylpiperazinyl)pyridine.

WO 00/12475 discloses indoline derivatives as 5-HT_{2b} and/or 5-HT_{2c} receptor ligands, especially for the treatment of obesity.

WO 00/12510 discloses pyrroloindoles, pyridoindoles and azepinoindoles as 5-HT_{2c} receptor agonists, particluarly for the treatment of obesity.

WO 00/12482 discloses indazole derivatives as selective, directly active 5-HT_{2c} receptor ligands, preferably 5-HT_{2c} receptor agonists, particularly for use as anti-obesity agents.

WO 00/12502 discloses pyrroloquinolines as 5-HT_{2c} receptor agonists, particularly for use as anti-obesity agents.

WO 00/35922 discloses 2,3,4,4*a*-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5(6*H*)ones as $5HT_{2c}$ agonists, which may be used for the treatment of obesity.

WO 00/44737 discloses aminoalkylbenzofurans as 5-HT_{2c} agonists, which may be used for the treatment of obesity.

Further compounds reported to be $5HT_{2c}$ receptor agonists are, for example, indazolylpropylamines of the type described in WO 00/12481; indazoles of the type described in WO 00/17170; piperazinylpyrazines of the type described in WO 00/76984; heterocycle fused γ-carbolines of the type described in WO 00/77001, WO 00/77002 and WO 00/77010; benzofurylpiperazines of the type described in WO 01/09111 and WO 01/09123; benzofurans of the type described in WO 01/09122; benzothiophenes of the type described in 01/09126; aminoalkylindazoles of the type described in WO 98/30548; indoles of the type described in WO 01/12603; indolines of the type described in WO 01/12602; pyrazino(aza)indoles of the type described in WO 00/44753 and tricyclic pyrroles or pyrazoles of the type described in WO 98/56768.

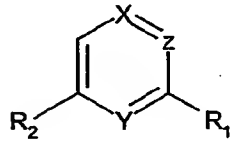
WO 96/11920 discloses CNS-active pyridinylurea derivatives.

WO 95/01976 discloses indoline derivatives active as 5-HT_{2c} antagonists and of potential use in the treatment of CNS disorders.

WO 99/58490 disloses aryl-hydronaphthalen-alkanamines which may effectuate partial or complete blockage of serotonergic 5-HT_{2c} receptors in an organism.

Summary of the Invention

According to the invention novel compounds of the general formula (I) are provided:



(I)

wherein

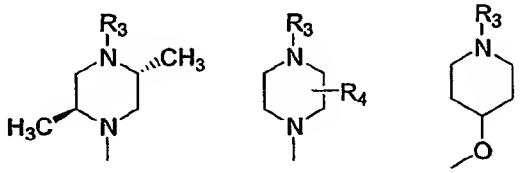
(i) X and Y represent both nitrogen and Z represents CH, forming a pyrazine derivative, or

(ii) X and Z represent both CH and Y represents nitrogen, forming a pyridine derivative, or

(iii) X represents C-CF_3, Z represents CH, and Y represents nitrogen, forming a 4-trifluoromethylpyridine derivative, or

(iv) Y and Z represent both nitrogen and X represents CH, forming a pyrimidine derivative, and wherein

R_1 and R_2 are each, independently, selected from a group A, consisting of



or from a group B, consisting of aryl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkoxy, aryloxy-C_2-C_6-alkoxy, heteroaryloxy-C_2-C_6-alkoxy, 1-indanyloxy, 2-indanyloxy, aryloxy, heteroaryloxy, arylthio, heteroarylthio, C_5-C_6-cycloalkylthio, C_5-C_8-alkoxy, C_5-C_8-alkylthio, C_3-C_6-alkynyloxy, C_3-C_6-alkenyloxy, fluoro-C_2-C_4-alkoxy, C_4-C_8-cycloalkyloxy, C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, halogen, aryl-C_1-C_4-alkylthio, heteroaryl-C_1-C_4-alkylthio, aryl-C_1-C_4-alkylamino, heteroaryl-C_1-C_4-alkylamino, heteroaryl and aryl;

with the proviso that:

(i) R_1 and R_2 are different and are not both selected from group A or group B at the same time;

(ii) when formula (I) is a pyrazine derivative R_1 or R_2 are other than, phenylthio, phenylmethylthio, phenyl or phenyl substituted by halogen;

(iii) R_1 in formula (I) is halogen, especially chloro, only when (I) is a pyrazine derivative and when R_2 simultaneously is 2-methylpiperazin-1-yl, 2-ethylpiperazin-1-yl or *trans*-2,5-dimethylpiperazin-1-yl;

(iv) when formula (I) is a pyrazine derivative and R_1 is 4-piperidinyloxy, R_2 is other than 3-pyridinylmethoxy, 4-quinolinylmethoxy, 2,4-dimethoxybenzyloxy and 3-(4-pyridinyl)propoxy;

(v) when both X and Z are CH and Y is N in formula (I), forming a pyridine derivative, and R_1 is 1-piperazinyl or 4-methylpiperazin-1-yl, then R_2 is other than, 2-phenylethyl, benzyloxy, benzylamino, phenylthio, phenoxy, substituted phenoxy, C_4-C_8-cycloalkyloxy and C_3-C_8-cycloalkylmethoxy;

(vi) when X is CH and Z and Y both are nitrogen in formula (I), forming a pyrimidine derivative, and R_2 is1-piperazinyl, then R_1 is other than phenoxy, phenyl or phenyl substituted by bromo, and C_5-C_8 alkoxy; and when R_2 is 4-methylpiperazin-1-yl or 4-(2-hydroxyethyl)piperazin-1-yl, then R_1 is other than 5-nitro-2-furyl;

(vii) when X is CH and Z and Y both are nitrogen in formula (I), forming a pyrimidine derivative, and R_1 is

1-piperazinyl, then R_2 is other than C_5-C_8 alkoxy;

and where

R_3 is H or C_{1-4}-alkyl, allyl, 2-hydroxyethyl, or 2-cyanoethyl, or a nitrogen protecting group, or a prodrug moiety such as an acyl- or an alkoxycarbonyl group forming a cleavable amide or carbamate linkage;

R_3 is preferably hydrogen;

R_4 is hydrogen or C_{1-4} alkyl, preferably hydrogen, methyl or ethyl, more preferably hydrogen or methyl;

and wherein any aryl or heteroaryl residue, alone or as part of another group, in R_1 or R_2 may be independently substituted in one or more positions, preferably one or two, by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{2-4}-acyl, C_{1-4}-alkylsulphonyl, cyano, nitro, hydroxy, C_{2-6}-alkenyl, C_{2-6}-alkynyl, fluoromethyl, trifluoromethyl, trifluoromethoxy, halogen, -N(R_5)(R_6), aryl, aryloxy, arylthio, aryl-C_{1-4}-alkyl, aryl-C_{2-4}-alkenyl, aryl-C_{2-4}-alkynyl, heteroaryl, heteroaryloxy, heteroarylthio or heteroaryl-C_{1-4}-alkyl, aryl-C_{1-4}-alkoxy, aryloxy-C_{1-4}-alkyl, dimethylamino-C_{2-4}-alkoxy;

and wherein any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in R_1 or R_2 in turn may be substituted in one or more postions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, trifluoromethyl, cyano, hydroxy or dimethylamino; and

R_5 and R_6 independently of each other are hydrogen, methyl or ethyl, or together with the nitrogen atom to which they are bound form a pyrrolidine, piperazine, morpholine, thiomorpholine or a piperidine ring;

and pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof.

When R_3 serves as a nitrogen protecting group R_3 is *t*-butoxycarbonyl (*t*-BOC), benzyl or trityl.

In case the compounds of formula (I) can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

In case the compounds of formula (I) contain groups, which may exist in tautomeric forms, the invention comprises the tautomeric forms of the compounds as well as mixtures thereof.

In case the compounds of formula (I) can be in the form of geometrical isomers, the invention comprises the geometrical isomers as well as mixtures thereof.

According to another aspect, the invention provides the compounds according to formula (I) above for use in therapy.

Still another aspect of the invention provides a pharmaceutical composition comprising a compound according to formula (I) above as the active ingredient,

preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

In yet another aspect, the invention provides a method for the treatment of a human or animal subject suffering from a serotonin-related disease, particularly 5-HT_{2C} receptor-related, especially eating disorders, particularly obesity; memory disorders, schizophrenia, mood disorders, anxiety disorders, pain, substance abuse, sexual dysfunctions, epilepsy, and urinary disorders.

Another aspect of the invention provides for the use of the compounds according to formula (I) above for the manufacture of a medicament for the treatment of a serotonin-related disease, particularly 5-HT_{2C} receptor-related, especially eating disorders, particularly obesity; memory disorders; schizophrenia, mood disorders, anxiety disorders, pain, substance abuse, sexual dysfunctions, epilepsy and urinary disorders.

Finally a method for modulating $5HT_{2C}$ receptor function is an aspect of the invention.

Detailed Description of the Invention

According to the present invention, a class of novel compounds has been developed which compounds bind to the 5-HT_{2C} receptor (agonists and antagonists) and which therefore may be used for the treatment of serotonin-related disorders.

First, the various terms used, separately and in combinations, in the above definition of the compounds having the general formula (I) will be explained.

By "heteroatom" is meant nitrogen, oxygen, sulphur, and in heterocyclic rings (including heteroaromatic as well as saturated and partially saturated heterocyclic rings), also selenium.

The term "aryl" is intended to include aromatic rings (monocyclic or bicyclic) having from 6 to 10 ring carbon atoms, such as phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydronaphthyl (can be linked to the remainder of the molecule via a carbon atom in any ring) and indanyl (can be linked to the remainder of the molecule via a carbon atom in any ring).

The term "heteroaryl" means a mono- or bicyclic aromatic ring system, only one ring need be aromatic, and which can be linked to the remainder of the molecule

via a carbon or nitrogen atom in any ring, and having from 5 to 10 ring atoms (mono- or bicyclic), in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur, oxygen and selenium. Examples of such heteroaryl rings are pyrrole, imidazole, thiophene, furan, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, oxadiazole, pyridine, pyrazine, pyrimidine, pyridazine, pyrazole, triazole, tetrazole, chroman, isochroman, coumarin, quinoline, quinoxaline, isoquinoline, phthalazine, cinnoline, quinazoline, indole, isoindole, indoline, isoindoline, benzothiophene, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, benzoxazole, 2,1,3-benzoxadiazole, benzothiazole, 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, benzimidazole, indazole, 2,3-dihydro-1,4-benzodioxine, 1,3-benzodioxole, 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2*H*-1,4-benzoxazine, 1,5-naphthyridine, 1,8-naphthyridine, 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine, and 2,3-dihydro-1,4-benzoxathiine. If a bicyclic aryl or heteroaryl ring is substituted, it may be substituted in any ring.

Exemplary aryl-C_1-C_6-alkyl, in which the alkyl portion of the group may be straight or branched, include benzyl, 2-phenylethyl, 3-phenyl-1-propyl, 1-phenylethyl, 1-phenyl-2-propyl and the like.

Exemplary aryl-C_1-C_6-alkoxy, in which the alkyl portion of the group may be straight or branched, include benzyloxy, 2-naphthylmethoxy, 2-phenylethoxy, 3-phenyl-1-propoxy, 1-phenylethoxy, 1-phenyl-2-propoxy, 2-phenyl-1-propoxy and the like.

Exemplary aryloxy-C_2-C_6-alkoxy, in which the alkyl portion of the group may be straight or branched, include 2-phenoxyethoxy, 2-(1-naphthyloxy)ethoxy, 3-(2- naphthyloxy)-1-propoxy, 3-phenoxy-1-propoxy, 4-phenoxy-1-butoxy, 5-phenoxy-1-pentoxy, 1-phenoxy-2-propoxy and the like.

Exemplary C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, in which the alkyl portion of the group may be straight or branched, include cyclopropylmethoxy, cyclopentylmethoxy, 2-cyclohexylethoxy, 1-cyclohexylethoxy, 1-cyclopropylethoxy, 1-cyclobutylethoxy and the like.

Exemplary heteroaryl-C_1-C_4-alkylamino include 2-(2-pyridinyl)ethylamino, 3-pyridinylmethylamino, 2-(2-thienyl)ethylamino, 2-(1*H*-indol-3-yl)ethylamino and the like.

Exemplary heteroaryloxy-C_2-C_6-alkoxy include 2-(8-quinolinyloxy)ethoxy, 2-(3-pyridinyloxy)ethoxy, 3-(8-quinolinyloxy)propoxy and the like

Exemplary C_3-C_6-alkynyloxy include propargyloxy, 1-hexynyloxy, 2-hexynyloxy, 3-butynyloxy, 3-pentynyloxy and the like.

C_{5-8}-alkoxy may be straight or branched. Exemplary alkoxy groups include pentyloxy, isopentyloxy, hexyloxy, and isohexyloxy.

Halogen includes fluorine, chlorine or bromine.

Where it is stated above that aryl and heteroaryl residues may be substituted (in one or more postions), this applies to aryl and heteroaryl *per se* as well as to any combined groups containing aryl or heteroaryl residues, such as heteroaryloxy-C_2-C_6-alkoxy, heteroaryloxy, aryl-C_1-C_6-alkoxy etc.

The term "*N*-oxides" means that one or more nitrogen atoms, when present in a compound, are in *N*-oxide form (N→O).

The term "prodrug forms" means a pharmacologically acceptable derivative, such as a carbamate or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15.

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

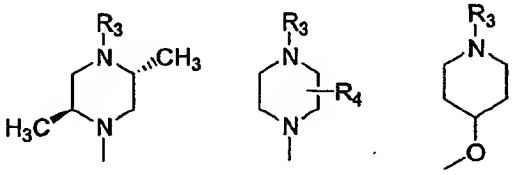
"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, toluenesulphonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like.

Preferred embodiments of the invention are:

– a compound of formula (I) wherein X and Y represent both nitrogen and Z represents CH, forming a pyrazine derivative;

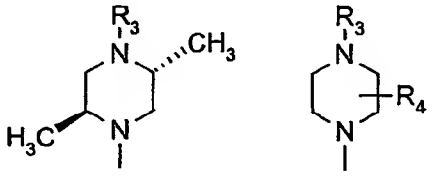
– a compound of formula (I) wherein Y and Z both represent nitrogen and X represents CH, forming a pyrimidine derivative;

– a compound of formula (I) wherein R_1 or R_2 is selected from



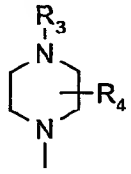
and wherein R_3 is hydrogen;

– a compound of formula (I) wherein R_1 or R_2 is selected from



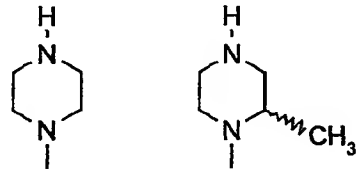
and where R_3 is hydrogen and R_4 is selected from hydrogen or methyl or ethyl;

– a compound of formula (I) wherein R_1 or R_2 is

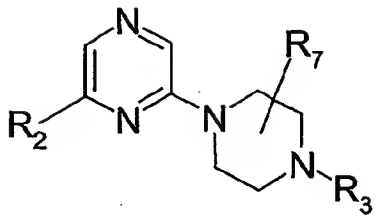


and where R_3 is hydrogen and R_4 is selected from hydrogen or methyl or ethyl; and

– a compound of formula (I) wherein R_1 or R_2 is selected from



In a further preferred embodiment, the compounds of formula (I) are selected from compounds in which X and Y both are nitrogen and Z is CH giving pyrazine derivatives of formula (II):



(II)

wherein

R_2 and R_3 are as defined above wherein any aryl and heteroaryl residue, alone or as part of another group, in R_2 in turn may be substituted in one or more positions, preferably one or two, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{2-4}-acyl, C_{1-4}-alkylsulphonyl, cyano, nitro, hydroxy, C_{2-6}-alkenyl, C_{2-6}-alkynyl, fluoromethyl, trifluoromethyl, trifluoromethoxy, halogen, -N(R_5)(R_6), aryl, aryloxy, arylthio, aryl-C_{1-4}-alkyl, aryl-C_{2-4}-alkenyl, aryl-C_{2-4}-alkynyl, heteroaryl, heteroaryloxy, heteroarylthio or heteroaryl-C_{1-4}-alkyl, aryl-C_{1-4}-alkoxy, aryloxy-C_{1-4}-alkyl, dimethylamino-C_{2-4}-alkoxy;

wherein any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in R_2 in turn may be substituted in one or more postions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, trifluoromethyl, cyano, hydroxy or dimethylamino;

R_5 and R_6 are as defined above; and

R_7 is hydrogen or C_{1-4} alkyl.

Another aspect of the invention is a compound of any of the formulae herein wherein R_3 is hydrogen; or wherein R_7 is hydrogen, methyl, or ethyl; or wherein R_7 is methyl and is attached to the C2-position of the piperazine ring; or wherein R_7 is hydrogen.

In formula (II), R_3 is preferably hydrogen, and R_7 is preferably hydrogen or C_{1-4}-alkyl. When R_7 is C_{1-4}-alkyl, it is most preferably substituted in the 2-postion of the piperazine ring. R_7 is most preferably hydrogen or methyl.

Preferred compounds of the general formula (I) above are:

2-(Benzyloxy)-6-(1-piperazinyl)pyrazine,

2-[(2-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,

2-[(3-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,

2-[(3,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-(1-Naphthylmethoxy)-6-(1-piperazinyl)pyrazine,
2-(1-Phenylethoxy)-6-(1-piperazinyl)pyrazine,
2-[1-(3-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[1-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-(3,4-Dihydro-2*H*-chromen-4-yloxy)-6-(1-piperazinyl)pyrazine,
2-(2-Phenylethoxy)-6-(1-piperazinyl)pyrazine,
2-[(2-Phenoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[2-(3-Chlorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(3-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(4-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(2,5-Dimethoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[(2-Phenylethyl)sulfanyl]-6-(1-piperazinyl)pyrazine,
2-[(5-Fluoro-2-methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(3-Cyanobenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(2-Chlorobenzyl)sulfanyl]-6-(1-piperazinyl)pyrazine,
2-[2-(4-Dimethylaminophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(1*H*-Indol-3-yl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(1*H*-Indol-1-yl)ethoxy]-6-(1-piperazinyl)pyrazine,
4-(Benzyloxy)-2-(1-piperazinyl)pyrimidine,
4-[(2-Methoxybenzyl)oxy]-2-(1-piperazinyl)pyrimidine,
2-{[3-(Benzyloxy)benzyl]oxy}-4-(1-piperazinyl)pyrimidine,
2-Benzyl-6-(1-piperazinyl)pyrazine,
2-[(3,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine,
1-[6-(Benzyloxy)-2-pyrazinyl]-2-ethylpiperazine
1-[6-(Benzyloxy)-2-pyrazinyl]-*trans*-2,5-dimethylpiperazine.
2-[2-(2-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-(2,3-Dihydro-1*H*-inden-1-ylmethoxy)-6-(1-piperazinyl)pyrazine
2-(4-Phenoxybutoxy)-6-(1-piperazinyl)pyrazine.
2-[(5-Phenoxypentyl)oxy]-6-(1-piperazinyl)pyrazine.
2-[(2,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine.

2-{[2-(2-Phenylethyl)benzyl]oxy}-6-(1-piperazinyl)pyrazine

(2*R*)-1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine,

2-[2-(2,6-Difluorophenoxy)ethoxy]-6-(1-piperazinyl)pyrazine

2-[2-(2-Naphthyloxy)ethoxy]-6-(1-piperazinyl)pyrazine

2-(1-Methyl-2-phenylethoxy)-6-(1-piperazinyl)pyrazine

2-{[2-(Phenoxymethyl)benzyl]oxy}-6-(1-piperazinyl)pyrazine

2-[(5-Fluoro-2-methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine

2-[(2,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine

2-[(2-Fluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine

2-(Benzo[*b*]thiophen-3-ylmethoxy)-6-(1-piperazinyl)pyrazine,

2-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-6-(1-piperazinyl)pyrazine,

2-[1-(2,6-Difluoro-phenyl)-ethoxy]-6-(1-piperazinyl)pyrazine,

2-(2-Naphthalen-2-yl-ethoxy)-6-(1-piperazinyl)pyrazine,

2-[3-(Naphthalen-2-yloxy)-propoxy]-6-(1-piperazinyl)pyrazine,

2-[2-(7-Methoxy-naphthalen-2-yloxy)-ethoxy]-6-(1-piperazinyl)pyrazine,

2-[5-(4-Chlorophenyl)-2-methylfuran-3-ylmethoxy]-6-(1-piperazinyl)pyrazine,

2-(1*H*-Indol-4-ylmethoxy)-6-(1-piperazinyl)pyrazine,

and their pharmacologically acceptable salts and solvates;

and

2-(Benzyloxy)-6-(1-piperazinyl)pyrazine,

2-[(2-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,

2-[(3-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,

2-[(3,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine,

2-(1-Naphthylmethoxy)-6-(1-piperazinyl)pyrazine,

2-(1-Phenylethoxy)-6-(1-piperazinyl)pyrazine,

2-[1-(3-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,

2-[1-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,

2-(3,4-Dihydro-2*H*-chromen-4-yloxy)-6-(1-piperazinyl)pyrazine,

2-(2-Phenylethoxy)-6-(1-piperazinyl)pyrazine,

2-[(2-Phenoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,

2-{[3-(Benzyloxy)benzyl]oxy}-6-(1-piperazinyl)pyrazine,

2-[2-(3-Chlorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,

2-[2-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,

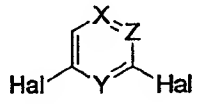
2-[2-(3-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(4-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(2,5-Dimethoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[(2-Phenylethyl)sulfanyl]-6-(1-piperazinyl)pyrazine,
2-[(5-Fluoro-2-methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(3-Cyanobenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(2-Chlorobenzyl)sulfanyl]-6-(1-piperazinyl)pyrazine,
2-[2-(4-Dimethylaminophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(1H-Indol-3-yl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(1H-Indol-1-yl)ethoxy]-6-(1-piperazinyl)pyrazine,
4-(Benzyloxy)-2-(1-piperazinyl)pyrimidine,
4-[(2-Methoxybenzyl)oxy]-2-(1-piperazinyl)pyrimidine,
2-{[3-(Benzyloxy)benzyl]oxy}-4-(1-piperazinyl)pyrimidine,
2-Benzyl-6-(1-piperazinyl)pyrazine,
2-[(3,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine,
and their pharmacologically acceptable salts and solvates.

As mentioned above, the compounds of the present invention are useful for the treatment (including prophylactic treatment) of serotonin-related disorders, especially 5-HT_{2c} receptor-related, in a human being or in an animal (including e.g. pets), such as eating disorders, especially obesity; memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders, including, but not restricted to, major depression and bipolar depression, including both mild and manic bipolar disorder, seasonal affective disorder (SAD); anxiety disorders, including situational anxiety, generalized anxiety disorder, primary anxiety disorders (panic disorders, phobias, obsessive-compulsive disorders, and post-traumatic stress disorders), and secondary anxiety disorders (for example anxiety associated with substance abuse); pain; substance abuse; sexual dysfunctions; epilepsy; and urinary disorders, such as urinary incontinence. Additionally, the compounds of the present invention are generally useful in treatment of diseases and disorders of the central nervous system (CNS).

The compounds of the present invention in radiolabelled form, may be used as a diagnostic agent.

This invention relates to methods of making compounds of any formulae herein comprising reacting any one or more of the compounds or formulae delineated herein including any processes delineated herein.

In one aspect, the invention is a method of making a compound of formula (I) delineated herein, taking a compound of the following formula:

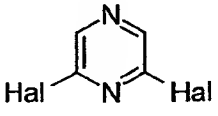


wherein; (i) X and Y represent both nitrogen and Z represents CH, forming a pyrazine derivative, or (ii) X and Z represent both CH and Y represents nitrogen, forming a pyridine derivative, or (iii) X represents C-CF_3, Z represents CH, and Y represents nitrogen, forming a 4-trifluoromethylpyridine derivative, or (iv) Y and Z represent both nitrogen and X represents CH, forming a pyrimidine deriviative, and wherein each Hal is independently a halogen; and reacting the compound with one or more chemical reagents in one or more steps to produce a compound of general formula (I) delineated herein.

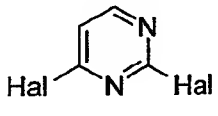
The compounds of general formula (I) above may be prepared by, or in analogy with, conventional methods, and especially according to or in analogy with the following methods.

Method A:

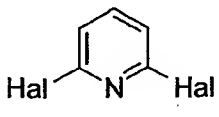
Compounds of formula (I) above in which R_1 (or R_2) are bound to the pyrazine-, pyridine- or pyrimidine ring in (I) via an O, S or N atom in R_1 (or R_2), are prepared by reacting a compound of the structural formula (III), (IV), (V), or (VI)



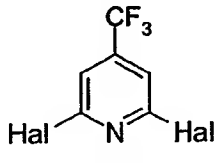
(III)



(IV)

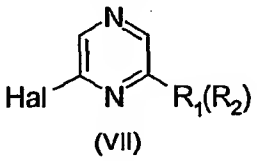


(V)

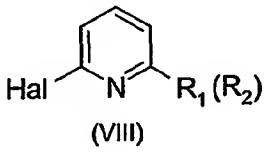


(VI)

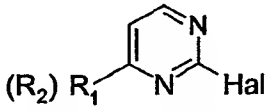
wherein Hal is halogen, with an appropriate amine, alcohol or thiol or its corresponding anion to produce a compound of formula (VII), (VIII), (IX), or (X):



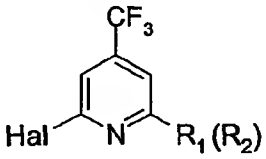
(VII)



(VIII)

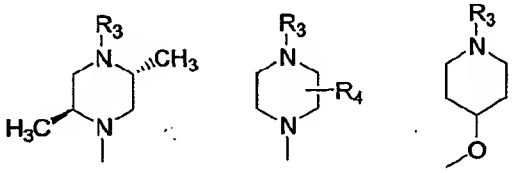


(IX)

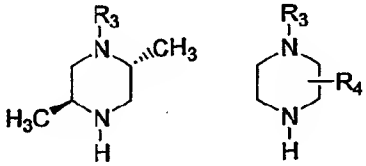


(X)

wherein R_1 (or R_2) is as defined above and with the proviso that R_1 (or R_2) is not any of the following groups



The appropriate alcohol, amine, or thiol may be converted completely or partially to its corresponding anion by treatment with bases, such as triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, K_2CO_3, NaOH, NaH, KO-*t*-Bu, lithium diisopropylamide or the like. The reaction is carried out in a solvent, such as dioxane, tetrahydrofuran, *tert*-butanol or *N,N*-dimethylformamide (DMF), at 0-200 °C for 1-24 hours. The compound of formula (VII), (VIII), (IX), or (X) is reacted with 1 to 10 molar equivalents of an appropriate amine selected from



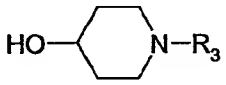
and where R_3 and R_4 are as defined above, in a solvent such as acetonitrile, dioxane, tetrahydrofuran, *n*-butanol, DMF, or in a mixture of solvents such as DMF/dioxane,

optionally in the presence of a base, such as K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOH, triethylamine, pyridine or the like, at 0-200 °C for 1-24 hours to produce the compound of formula (I). When R_3 is a nitrogen protecting group as defined above, the subsequent

N-deprotection is carried out by conventional methods such as those described in Protective Groups in Organic Synthesis, John Wiley & Sons, 1991 or subsequent editions thereof.

Method B:

Compounds of formula (I) are prepared by reacting a compound of formula (VII), (VIII), (IX) or (X) above with a 4-hydroxysubstituted piperidine compound of formula (XI)



(XI)

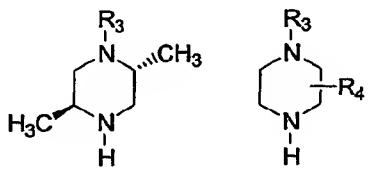
wherein R_3 is as defined above.

The reaction is carried out in a solvent, such as toluene, DMF, *tert*-butanol or dioxane, in the presence of a base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, KOH, KO-*t*-Bu, NaH or the like, at 0-200 °C for 1-24 hours.

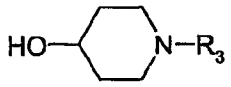
The nitrogen atom in (XI) may be protected with a suitable protecting group, preferably *tert*-butoxycarbonyl, trityl or benzyl. *N*-Deprotection is then carried out by conventional methods such as those described in Protective Groups in Organic Synthesis, John Wiley & Sons, 1991 or subsequent editions thereof.

Method C:

Compounds of formula (I) are prepared by reacting a compound of formula (III), (IV), (V), or (VI) above with an appropriate amine, selected from

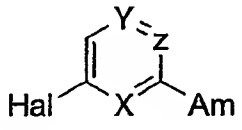


or a 4-hydroxysubstituted piperidine compound (XI)

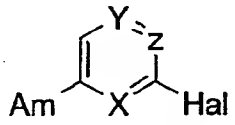


(XI)

and where R_3 and R_4 are as defined above to produce a compound of formula (XII) or (XIII):

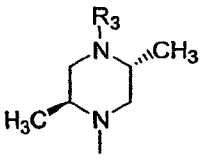


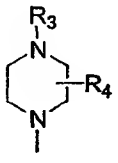
(XII)

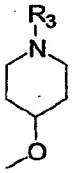


(XIII)

wherein Hal is as defined above, and X, Y, Z have the same meaning as in formula (I), and Am is an amine residue selected from





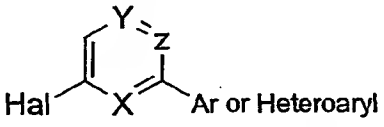


and where R_3 and R_4 are as defined above. The reaction conditions may be those described for methods A and B above. The compound of formula (XII) or (XIII) is reacted with an appropriate alcohol, amine (other than those defined for Am above) or thiol or its corresponding anions to produce a compound of the formula (I). The reaction conditions may be those described for method A above. When R_3 is a nitrogen protecting group as defined above, the subsequent *N*-deprotection is carried out by conventional methods such as those described in Protective Groups in Organic Synthesis, John Wiley & Sons, 1991 or subsequent editions thereof.

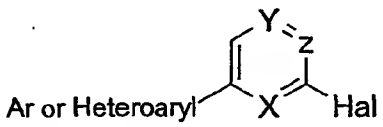
Method D.

According to another general process (the Suzuki reaction; for a review, see: Chem. Rev. 1995, 95, 2457-2483), the compounds of formula (I) wherein R_1 or R_2 are aryl or heteroaryl may be prepared by reacting a compound of formula (III), (IV), (V), or (VI) with a boronic acid derivative of the type heteroaryl-$B(OH)_2$ or aryl-$B(OH)_2$, where heteroaryl and aryl are as defined above, in the presence of a transition metal

catalyst such as $(Ph_3P)_4Pd$, where Ph represents phenyl, in a suitable solvent such as an ether (e.g., 1-2-dimethoxyethane or tetrahydrofuran), in the presence or absence of water, or an aromatic hydrocarbon (e.g., toluene). The reaction is preferably carried out in the presence of a base such as an alkali or alkaline earth metal carbonate (e.g, sodium carbonate) at a suitable temperature up to reflux to provide a compound of formula (XIV) or (XV)

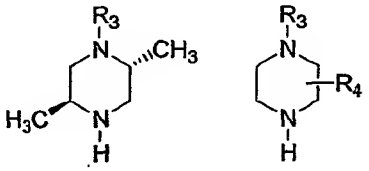


(XIV)

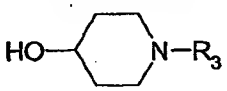


(XV)

The compound of formula (XIV) or (XV) is reacted with 1 to 10 molar equivalents of an appropriate amine selected from



or a 4-hydroxysubstituted piperidine compound (XI)



(XI)

to produce a compound of formula (I) and where R_3 and R_4 are as defined above. The reaction conditions may be those described for methods A and B above.

Method E. A compound of formula (XII) or (XIII) is reacted with a boronic acid derivative heteroaryl-$B(OH)_2$ or aryl-$B(OH)_2$ to provide a compound of formula (I). Heteroaryl and aryl are as defined above. The reaction conditions may be those described in method D.

An obtained compound of formula (I) may be converted to another compound of formula (I) by methods well known in the art.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically

acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are maleic acid, fumaric acid, succinic acid, methanesulfonic acid, acetic acid, oxalic acid, benzoic acid, hydrochloric acid, sulphuric acid, phosphoric acid, and the like.

The compounds of formula (I) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g. as a pure enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral columns.

The necessary starting materials for preparing the compounds of formula (I) are either known or may be prepared in analogy with the preparation of known compounds.

In accordance with the present invention, the compounds of formula (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as are well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous, subcutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, pills, capsules, powders, syrups, elixirs, dispersable granules, cachets, suppositories and the like, in the form of sterile

solutions, suspensions or emulsions for parenteral administration, sprays, e.g. a nasal spray, transdermal preparations, e.g. patches, and the like.

As mentioned above, the compounds of the invention may be used for the treatment of serotonin-related disorders in a human being or an animal, such as eating disorders, particularly obesity, memory disorders, schizophrenia, mood disorders, anxiety disorders, pain, substance abuse, sexual dysfunctions, epilepsy, and urinary disorders. The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

The invention will now be illustrated with the following examples, which however, are for illustrative purposes are not intended to limit the scope of the invention.

EXAMPLES

General:

The structures of the prepared compounds were confirmed by standard spectroscopical methods, and elemental analysis and/or high resolution MS. The NMR data were obtained on a JEOL JNM-EX 270, a Bruker 400 DPX or a Bruker DRX 500 spectrometer. IR spectra were obtained on a Perkin Elmer SPECTRUM 1000 FT-IR spectrometer. High resolution MS was obtained on a Micromass LCT spectrometer. Elemental analysis was performed by Mikro Kemi AB, Uppsala, Sweden or at Pharmacia AB, Stockholm, Sweden. Melting points, when given, were obtained on a Büchi or a Gallenkamp melting point apparatus and are uncorrected.

EXAMPLE 1

2-(1-Naphthylmethoxy)-6-(1-piperazinyl)pyrazine.

To a solution of 2,6-dichloropyrazine (298 mg, 2.00 mmol) and 1-naphthylmethanol (348 mg, 2.20 mmol) in dioxane (5 mL) was added NaH (55 % in mineral oil, 96 mg, 2.2 mmol) at room temperature. The reaction was stirred at room temperature and monitored by GC. After 3 h, piperazine (189 mg, 2.20 mmol) and NaH (55% in oil, 96 mg, 2.2 mmol) was added into the reaction flask at room temperature. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated off. To the residue was added piperazine (671 mg, 7.80 mmol) and acetonitrile (5 mL) and the solution was heated under reflux for 5 h. The reaction mixture was directly loaded on a short column of silica gel for flash column chromatography. Elution with MeOH/dichloromethane (1:9) furnished 0.41 g (64%) of the title compound. HRMS *m/z* calcd for $C_{19}H_{20}N_4O$ $(M)^+$ 321.1715, found 321.1721. Anal. ($C_{19}H_{20}N_4O \cdot 0.1\ H_2O$) C, H, N.

EXAMPLE 2

2-[1-(3-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-[1-(3-fluorophenyl)ethoxy]pyrazine.

To a solution of 2,6-dichloropyrazine (298 mg, 2.00 mmol) and 1-(3-fluorophenyl)ethanol (308 mg, 2.2 mmol) in dioxane (5 mL) was added NaH (55 % in oil, 96 mg, 2.2 mmol) at room temperature. The reaction mixture was stirred over night. Water (0.5 mL) was added and the mixture was stirred for 15 min. Drying (K_2CO_3), filtration, and concentration *in vacuo* gave the title compound as an oil (0.55 g) that was used directly in the next step. MS *m/z* 254 $(M+H)^+$.

Step 2: 2-[1-(3-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (crude, 1.09 g, ~ 4.3 mmol), piperazine (1.03 g, 12.0 mmol) and K_2CO_3 (1.00 g, 7.2 mmol) in acetonitrile (5 mL) was heated under reflux overnight (20 h). After cooling, ethyl acetate (15 mL) and water (5 mL) were added. The ethyl acetate layer was filtered through a short column of silica gel using MeOH/ethyl ether (1:1) as eluent to give 0.72 g (55%) of the title compound as

an oil. HRMS *m/z* calcd for $C_{16}H_{19}N_4O_4F$ $(M)^+$ 302.1543, found 302.1528. Anal. ($C_{16}H_{19}N_4OF \cdot 0.5\ H_2O$) C, H, N.

EXAMPLE 3

2-(1,3-Benzodioxol-5-ylmethoxy)-6-(1-piperazinyl)pyrazine, Acetate.

Step 1: 2-(1,3-Benzodioxol-5-ylmethoxy)-6-chloropyrazine.

To a solution of 2,6-dichloropyrazine (298 mg, 2.00 mmol) and piperonyl alcohol (335 mg, 2.20 mmol) in dioxane (5 mL) was added NaH (55 % in mineral oil, 96 mg, 2.2 mmol) at room temperature. The reaction mixture was stirred overnight. Water (0.5 mL) was added and the mixture was stirred for 15 min. Drying, Na_2CO_3, filtration and concentration *in vacuo* furnished an oil (0.54 g) that was used directly in the next step. HRMS *m/z* calcd for $C_{12}H_9ClN_2O_3$ $(M)^+$ 264.0302, found 264.0303.

Step 2: 2-(1,3-Benzodioxol-5-ylmethoxy)-6-(1-piperazinyl)pyrazine, Acetate.

A mixture of the product from step 1 above (0.54 g, 2.0 mmol), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.2 mmol) in acetonitrile (5 mL) was heated under reflux for 5 h. After cooling, ethyl acetate (20 mL) and water (5 mL) were added. The saved ethyl acetate layer was filtered through a short column of silica gel using methanol/ethyl ether (1:1) as eluent. This furnished the free base of the title compound as an oil (0.43 g). This material was dissolved in methanol and acetic acid (0.5 mL) was added. The solution was concentrated. Diethyl ether (25 mL) was added and the flask was shaken until crystallization started. The crystals was collected, washed with diethyl ether and dried in air to give 0.34 g (45%) of the title compound: mp 124–127 °C. HRMS *m/z* calcd for $C_{16}H_{18}N_4O_3$ $(M)^+$ 314.1379, found 314.1308. Anal. ($C_{16}H_{18}N_4O_3 \cdot CH_3COOH \cdot 1.6H_2O$) C, H, N.

EXAMPLE 4

2-[(3-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetate.

Step 1: 2-Chloro-6-[(3-methoxybenzyl)oxy]pyrazine.

To a solution of 2,6-dichloropyrazine (444 mg, 3.00 mmol) and 3-methoxybenzyl alcohol (455 mg, 3.30 mmol) in dioxane (5 mL) was added NaH (55 % in oil, 144 mg, 3.30 mmol) at room temperature. The reaction mixture was stirred overnight.

Water (0.5 mL) and ethyl acetate (10 mL) were added and the mixture was stirred for 15 min and then filtered. The filtrate was dried over K_2CO_3 and concentrated to give an oil (0.86 g) that was used directly in the next step. MS *m/z* 250 $(M+H)^+$.

Step 2: 2-[(3-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetate.
A mixture of the product from step 1 above (0.57 g, ~ 2.0 mmol), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.2 mmol) in acetonitrile (5 mL) was heated under reflux for 10 h. After cooling, ethyl acetate (30 mL) was added. The ethyl acetate layer was washed with water and brine, dried over Na_2CO_3, and concentrated under reduced pressure. The residue was dissolved in diethyl ether. Acetic acid (0.5 mL) was added and the solution was left at room temperature for crystallization. The crystals were collected, washed with diethyl ether and dried in vaccum to give 0.54 g (75%) of the title compound: mp 111-113 °C. HRMS *m/z* calcd for $C_{16}H_{20}N_4O_2$ $(M)^+$ 300.1586, found 300.1589. Anal. ($C_{16}H_{20}N_4O_2 \cdot CH_3COOH$) C, H, N.

EXAMPLE 5

2-[(2-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Dihydrochloride.

Step 1: 2-Chloro-6-[(2-methoxybenzyl)oxy]pyrazine.
The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (298 mg, 2.00 mmol), 2-methoxybenzyl alcohol (303 mg, 2.20 mmol) and NaH (55 % in mineral oil, 96 mg, 2.2 mmol). The yield of the crude product was 0.49 g (98%) and was used directly as such in the next step. MS *m/z* 250 $(M)^+$. HRMS *m/z* calcd for $C_{12}H_{11}ClN_2O_2$ $(M)^+$ 250.0509, found 250.0522.

Step 2: 2-[(2-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Dihydrochloride.
The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.49 g), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.2 mmol). This gave the free base of the title compound as an oil. Yield 0.43 g (73%). The free base was dissolved in ethyl ether and a solution of HCl in diethyl ether was added until no more precipitate was formed. The precipitate was collected, washed with diethyl ether, and dried in vaccum to give 0.41 g (56%) of the

title compound: mp 171-173 °C). HRMS *m/z* calcd for $C_{16}H_{20}N_4O_2$ $(M)^+$ 300.1586, found 300.1586. Anal. ($C_{16}H_{20}N_4O_2 \cdot 2HCl$) C, H, N.

EXAMPLE 6

2-[(3,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetate.

Step 1: 2-Chloro-6-[(3,5-difluorobenzyl)oxy]pyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol), 3,5-difluorobenzyl alcohol (475 mg, 3.30 mmol) and NaH (55% in mineral oil, 144 mg, 3.30 mmol). The solid product was collected, washed with water, and dried to give 0.77 g (100%) of the crude product that was used directly in the next step. An analytical sample was recrystallized from diethyl ether/hexane: mp 70-71 °C. MS *m/z* 257 $(M+H)^+$. Anal. ($C_{11}H_7ClFN_2O$) C, H, N.

Step 2: 2-[(3,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.51 g, ~ 2.0 mmol), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.2 mmol). Yield 0.49 g, (67%); mp 70-72 °C; HRMS *m/z* calcd for $C_{15}H_{16}F_2N_4O$ $(M)^+$ 306.1292, found 306.1292. Anal. ($C_{15}H_{16}F_2N_4O \cdot CH_3COOH \cdot H_2O$) C, H, N.

EXAMPLE 7

2-([1,1'-Biphenyl]-4-ylmethoxy)-6-(1-piperazinyl)pyrazine, Acetate.

Step 1: 2-([1,1'-Biphenyl]-4-ylmethoxy)-6-chloropyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol), *p*-phenylbenzyl alcohol (607 mg, 3.30 mmol) and NaH (55% in mineral oil, 144 mg, 3.30 mmol). Recrystallization from hexane gave 0.55 g (88%) of the title compound: mp 86-87 °C. MS *m/z*: 297 $(M+H)^+$. Anal. ($C_{17}H_{13}ClN_2O$) C, H, N.

Step 2: 2-([1,1'-Biphenyl]-4-ylmethoxy)-6-(1-piperazinyl)pyrazine, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.54 g, 1.87 mmol), piperazine (0.86 g, 10.0 mmol) and K_2CO_3 (1.00 g, 7.2 mmol). Yield: 0.35 g (44%); mp 102-104 °C. HRMS *m/z* calcd for $C_{21}H_{22}N_4O$ $(M)^+$ 346.1794, found 346.1777. Anal. ($C_{21}H_{22}N_4O \cdot CH_3COOH \cdot 0.55H_2O$) C, H, N.

EXAMPLE 8

2-[2-(3-Chlorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Acetate.

Step 1: 2-Chloro-6-[2-(3-chlorophenyl)ethoxy]pyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol) and *m*-chlorophenethyl alcohol (515 mg, 3.30 mmol) and NaH (55% in mineral oil, 144 mg, 3.30 mmol). The crude product (0.92 g) was used directly in the next step. MS *m/z* 269 $(M+H)^+$.

Step 2: 2-[2-(3-Chlorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.81 g, 3.02 mmol), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.2 mmol). Yield: 0.75 g (65%); mp 118-119 °C. HRMS *m/z* calcd for $C_{16}H_{19}ClN_4O$ $(M)^+$ 318.1247, found 318.1249. Anal. ($C_{16}H_{19}ClN_4O \cdot CH_3COOH$) C, H, N.

EXAMPLE 9

6-(1-Piperazinyl)-2-pyrazinyl 1,2,3,4-tetrahydro-1-naphthalenyl ether, Acetate.

Step 1: 2-Chloro-6-(1,2,3,4-tetrahydro-1-naphthalenyloxy)pyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol) and 1,2,3,4-tetrahydro-1-naphthol (488 mg, 3.30 mmol) and NaH (55% in oil, 144 mg, 3.30 mmol). The crude product (0.86 g) was used directly in the next step. MS *m/z* 261 $(M+H)^+$.

Step 2: 6-(1-Piperazinyl)-2-pyrazinyl 1,2,3,4-tetrahydro-1-naphthalenyl ether, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.75 g, 2.88 mmol), piperazine (0.86 g, 10

mmol) and K_2CO_3 (1.00 g, 7.2 mmol). Yield: 0.59 g (55%); mp 160-162 °C. MS *m/z* 310 $(M)^+$. HRMS *m/z* calcd for $C_{18}H_{22}N_4O$ $(M)^+$ 310.1794, found 310.1799. Anal. ($C_{18}H_{22}N_4O \cdot CH_3COOH$) C, H, N.

EXAMPLE 10

2-(1-Piperazinyl)-6-{[4-(trifluoromethyl)benzyl]oxy}pyrazine, Acetate.

Step 1: 2-Chloro-6-{[4-(trifluoromethyl)benzyl]oxy}pyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol) and 4-trifluoromethylbenzyl alcohol (581 mg, 3.30 mmol) and NaH (55% in mineral oil, 144 mg, 3.30 mmol). Recrystallization from hexane gave 0.81 g (93%) of the title compound: mp 67-69 °C.

MS *m/z* 289 $(M+H)^+$. Anal. ($C_{12}H_8ClF_3N_2O$) C, H, N.

Step 2: 2-(1-Piperazinyl)-6-{[4-(trifluoromethyl)benzyl]oxy}pyrazine, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.54 g, 1.89 mmol), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.20 mmol). Yield: 0.36 g (48%); mp 84-85 °C. MS *m/z* 338 $(M)^+$. HRMS *m/z* calcd for $C_{16}H_{17}F_3N_4O$ $(M)^+$ 338.1054, found 338.1063. Anal. ($C_{16}H_{17}ClF_3N_4O \cdot CH_3COOH$) C, H, N.

EXAMPLE 11

2-(1-Piperazinyl)-6-(3-pyridinylmethoxy)pyrazine, Acetate.

Step 1: 2-Chloro-6-(3-pyridinylmethoxy)pyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol), nicotinic alcohol (360 mg, 3.30 mmol) in dioxane (5 mL) and NaH (55 % in oil, 144 mg, 3.30 mmol). The crude product, obtained as an oil (0.72 g), was used directly in the next step. MS *m/z* 221 $(M)^+$.

Step 2: 2-(1-Piperazinyl)-6-(3-pyridinylmethoxy)pyrazine, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.74 g, 3.35 mmol), piperazine (0.86 g, 10

mmol) and K_2CO_3 (1.00 g, 7.2 mmol). Yield: 0.73 g (44 %); mp 98-99 °C; MS *m/z* 271$(M)^+$. HRMS *m/z* calcd for $C_{14}H_{17}N_5O$ $(M)^+$ 271.1433, found 271.1425. Anal. ($C_{14}H_{17}N_5O \cdot CH_3COOH$) C, H, N.

EXAMPLE 12

2-(1-Piperazinyl)-6-[2-(3-pyridinyl)ethoxy]pyrazine, Acetate.

Step 1: 2-Chloro-6-[2-(3-pyridinyl)ethoxy]pyrazine.

The title compound was prepared according to the procedure of example 4, step 1 starting from 2,6-dichloropyrazine (444 mg, 3.00 mmol) and 2-(3-pyridyl)ethanol (405 mg, 3.30 mmol) and NaH (55% in mineral oil, 144 mg, 3.30 mmol). The crude product, obtained as an oil (0.62 g, 88% yield), was used directly in the next step. MS *m/z* 235 $(M)^+$.

Step 2: 2-(1-Piperazinyl)-6-[2-(3-pyridinyl)ethoxy]pyrazine, Acetate.

The title compound was prepared according to the procedure of example 4, step 2 starting from the product of step 1 above (0.62 g, 2.64 mmol), piperazine (0.86 g, 10 mmol) and K_2CO_3 (1.00 g, 7.2 mmol). Yield: 0.40 g (44%); mp 90-91 °C. MS *m/z* 285 $(M)^+$. HRMS *m/z* calcd for $C_{15}H_{19}N_5O$ $(M)^+$ 285.1590, found 285.1598. Anal. ($C_{15}H_{19}N_5O \cdot CH_3COOH$) C, H, N.

EXAMPLE 13

2-(2-Furylmethoxy)-6-(1-piperazinyl)pyrazine.

Step 1: *tert*-Butyl 4-(6-chloro-2-pyrazinyl)-1-piperazinecarboxylate.

A mixture of *tert*-butyl 1-piperazinecarboxylate (5.07 g, 27.2 mmol), 2,6-dichloropyrazine (3.38 g, 22.7 mmol), and K_2CO_3 (4.09 g, 30.0 mmol) in acetonitrile (20 mL) was stirred at 65 °C for 12.5 h and for a further 15 h at room temperature. Ether was added and the suspension was filtered. Concentration *in vacuo* furnished the crude product as an oil that crystallized upon standing. Purification by chromatography on silica gel using ethyl acetate/*n*-hexane (6:4) as eluent gave 6.1 g (90%) of the title compound as a solid. HRMS *m/z* calcd for $C_{13}H_{19}ClN_4O_2$ $(M)^+$ 298.1197, found 298.1211. Anal. ($C_{13}H_{19}ClN_4O_2$) C, H, N.

Step 2: 6-Chloro-2-(1-piperazinyl)pyrazine.*

A solution of trifluoroacetic acid (TFA; 6 mL) in dichloromethane (24 mL) was added to a stirred solution of the product of step 1 above (5.79 g, 19.4 mmol) in dichloromethane (20 mL) at 0 °C. After 1 h and 1.5 h of stirring, additional portions (10 mL and 5 mL) of TFA were added. Crushed ice and 5 M aqueous NaOH were added and the mixture was extracted with dichloromethnae (12 x 200 mL). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. This furnished 3.48 g (90%) of the title compound as a light yellow solid.

*Previously described in a) J. Med. Chem. 1978, *21*, 536-542; b) US 4,082,844

Step 3: 2-(2-Furylmethoxy)-6-(1-piperazinyl)pyrazine.

K-*t*-BuO (1.55 g, 13.8 mmol) was added to a mixture of the product from step 2 above

(1.40 g, 7.05 mmol) and 2-furanmethanol (5.3 g, 54 mmol). After being stirred for 7.5 h at 110 °C, the mixture was applied onto a bed of silica (16 x 6 cm). Elution with $CHCl_3$/MeOH (95:5 followed by 90:10) furnished 1.35 g (74%) of the title compound as an oil. HRMS *m/z* calcd for $C_{13}H_{16}N_4O_2$ $(M)^+$ 260.1273, found 260.1276. Anal. ($C_{13}H_{16}N_4O_2$) C, H, N.

EXAMPLE 14

2-(2-Phenylethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

K-*t*-BuO (0.80 g, 7.13 mmol) was added to a mixture of the product from example 13, step 2 (0.638 g, 3.21 mmol) and 2-phenylethanol (5.62 g, 46.0 mmol). After being stirred for 5 h at 105 °C in a sealed flask, the mixture was applied onto a bed of silica (16 x 5 cm). Elution with $CHCl_3$/MeOH (97:3 followed by 90:10) furnished 0.68 g of an thick beige colored oil. This material was redissolved in ethyl acetate and K_2CO_3 was added. Filtration and concentration *in vacuo* furnished 0.67 g (74%) of the free base of the title compound as an oil. HRMS *m/z* calcd for $C_{16}H_{20}N_4O$ $(M)^+$ 284.1637, found 284.1630. The free base was converted into its maleate salt which was recrystallized from MeOH/ether: mp 166-168 °C. Anal. ($C_{16}H_{20}N_4O \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 15

2-(2-Furyl)-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-(2-furyl)pyrazine.

1,2-Dimethoxyethane (130 mL) was added to a mixture of tetrakis(triphenylphosphine)palladium (0) (0.93 g, 0.80 mmol) and 2,6-dichloropyrazine (2.55 g, 17.1 mmol). After 5 min of stirring at room temperature, furan-2-boronic acid (1.91 g, 17.1 mmol) followed by aqueous Na_2CO_3 (30 mL; 2 M) were added. The mixture was heated at reflux for 1 h [TLC monitoring by SiO_2/*n*-hexane/ethyl acetate (90:10)]. The layers were separated and the light brownish water layer was extracted with dichloromethane (2 x 200 mL). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. The brown-yellow oil obtained was purified by silica gel chromatography (18.5 x 4 cm) eluting with *n*-hexane/ethyl acetate (90:10). This furnished 1.47 g (48%) of the title compound as a light yellow solid. HRMS *m/z* calcd for $C_8H_5ClN_2O$ $(M)^+$ 180.0090, found 180.0092. Anal. ($C_8H_5ClN_2O$) C, H, N.

Step 2: 2-(2-Furyl)-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (0.94 g, 5.2 mmol), piperazine (1.28 g, 14.9 mmol, K_2CO_3 (0.87 g, 6.3 mmol) in acetonitrile (5 mL) was heated in a sealed pyrex flask at 85 °C for 3 h. The mixture was diluted with dichloromethane, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel chromatography (18 x 4 cm) to furnish a yellow oil. This material was redissolved in a small volume of $CHCl_3$/ether (9:1) and filtered through a short (4 cm) plug of alumina eluting with ether/MeOH (96:4). The filtrate was concentrated *in vacuo* to afford 0.77 g (64%) of the title compound as a light yellow solid. HRMS *m/z* calcd for $C_{12}H_{14}N_4O$ $(M)^+$ 230.1168, found 230.1170. Anal. ($C_{12}H_{14}N_4O$) C, H, N.

EXAMPLE 16

2-(1-Piperazinyl)-6-(3-thienyl)pyrazine.

Step 1: 2-Chloro-6-(3-thienyl)pyrazine.

1,2-Dimethoxyethane (120 mL) was added to a mixture of tetrakis(triphenylphosphine)palladium (0) (0.87 g, 0.75 mmol) and 2,6-dichloropyrazine (2.43 g, 16.3 mmol). After 15 min of stirring at room temperature, thiophene-3-boronic acid (2.09 g, 16.3 mmol) followed by aqueous Na_2CO_3 (2 M; 25 mL) were added. The mixture was heated at reflux for 2 h [TLC monitoring by SiO_2/*n*-hexane/ethyl acetate (85:15)]. The layers were separated and the light brownish water layer was extracted with ether (2 x 100 mL). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. The brownish oil obtained was purified by silica gel chromatography (18 x 5 cm) eluting with *n*-hexane/ethyl acetate (85:15). This furnished 1.46 g (45%) of the title compound as an off-white solid. HRMS *m/z* calcd for $C_8H_5ClN_2S$ $(M)^+$ 195.9862, found 195.9868. Anal. ($C_8H_5ClN_2S$) C, H, N.

Step 2: 2-(1-Piperazinyl)-6-(3-thienyl)pyrazine.

A mixture of the product from step 1 above (1.04 g, 5.29 mmol), piperazine (1.32 g, 15.3 mmol), and K_2CO_3 (0.81 g, 5.82 mmol) in acetonitrile (6 mL) was heated in a sealed pyrex flask at 85 °C for 8.5 h. The reaction mixture was diluted with dichloromethane, filtered, and concentated *in vacuo*. The semi-solid residue was purified by column chromatography on silica gel (18 x 5 cm) using $CHCl_3$/MeOH (9:1) as eluent to furnish an oil. This material was redissolved in ethyl acetate, filtered, and concentrated *in vacuo*. This gave 0.98 g (75%) of the title compound as a yellow sticky oil. HRMS *m/z* calcd for $C_{12}H_{14}N_4S$ $(M)^+$ 246.0939, found 246.0943. Anal. ($C_{12}H_{14}N_4S$) C, H, N.

EXAMPLE 17

***N*-Benzyl-6-(1-piperazinyl)-2-pyrazinamine.**

Step 1: *N*-Benzyl-6-chloro-2-pyrazinamine.

A mixture of 2,6-dichloropyrazine (1.31 g, 8.8 mmol), benzylamine (1.15 g, 10.7 mmol) and K_2CO_3 (1.65 g, 11.9 mmol) in acetonitrile (6 mL) was heated at 85 °C for

13 h in a sealed pyrex flask. The reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The yellow solid residue was dissolved in a small volume of methanol and purified by silica gel chromatography (18 x 4 cm) using $CHCl_3$/MeOH (98:2) as eluent. A second purification (SiO_2; 16 x 4 cm) using $CHCl_3$ as eluent furnished 1.55 g (81%) of the title compound as a light yellow solid. HRMS *m/z* calcd for $C_{11}H_{10}ClN_3$ $(M)^+$ 219.0563, found 219.0568. Anal. ($C_{11}H_{10}ClN_3$) C, H, N.

Step 2: *N*-Benzyl-6-(1-piperazinyl)-2-pyrazinamine.

A mixture of the product from step 1 above (1.25 g, 5.7 mmol), piperazine (1.0 g, 11.6 mmol), and K_2CO_3 (1.0 g, 7.3 mmol) in dioxane (3 mL) was heated at 160 °C for 11 h in a sealed pyrex flask. The reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The red-brownish residue was dissolved in a small volume of $CHCl_3$/MeOH (9:1) and purified by silica gel chromatography (15 x 4 cm) using $CHCl_3$/MeOH (95:5, followed by 9:1) as eluent. The free base was obtained as a brownish solid (0.9 g, 3.33 mol) that was redissolved in methanol (10 mL). Maleic acid (0.45 g, 3.83 mmol) in methanol (5 mL) was added and the salt was precipitated out by addition of ether. The salt was recrystallized from MeOH-ether and finally converted back to the free base by alkalinization (10% aqueous Na_2CO_3) and extraction with ether (5 x 60 mL). The combined ether layers were dried (K_2CO_3), filtered and concentrated. This furnished 0.36 g (23%) of the title compound as a light yellow powder. HRMS *m/z* calcd for $C_{15}H_{19}N_5$ $(M)^+$ 269.1640, found 269.1641. Anal. ($C_{15}H_{19}N_5$) C, H, N.

EXAMPLE 18

1-[6-(2-Thienylmethoxy)-2-pyridinyl]piperazine.

Step 1: 2-Chloro-6-(2-thienylmethoxy)pyridine.*

K-*t*-BuO (1.70 g, 15.1 mmol) was added portionwise to a stirred mixture of 2-thiophenemethanol (2.14 g, 18.7 mmol) and 2,6-dichloropyridine (2.13 g, 14.4 mmol) in dioxane (3 mL) at room temperature. An exotermic reaction started and more dioxane (3 mL) was added. After 3 h of stirring at room temperature, the

reaction mixture was passed through a column of silica using *n*-hexane/ethyl acetate (85:15) as eluent. A second purification on silica (16 x 4 cm) using *n*-hexane/ethyl acetate (9:1) furnished 3.0 g (93%) of the title compound as a light beige oil. HRMS *m/z* calcd for $C_{10}H_8ClNOS$ $(M)^+$ 225.0015, found 225.0022. Anal. ($C_{10}H_8ClNOS$) C, H, N. *Previously described in EP 693490.

Step 2: 1-[6-(2-Thienylmethoxy)-2-pyridinyl]piperazine.

A mixture of the product from step 1 above (1.35 g, 5.98 mmol), piperazine (1.55 g, 17.9 mmol) and K_2CO_3 (0.91 g, 6.58 mmol) in acetonitrile (5 mL) was heated at 125 125 °C for 6.5 h in a sealed pyrex flask. The reaction mixture was diluted with dichlorometane, filtered and concentrated *in vacuo*. The semi-solid residue was purified by silica gel (16 x 4 cm) chromatography using $CHCl_3$/MeOH (9:1) as eluent. Solvents were evaporated and the oily residue was redissolved in $CHCl_3$/ether (1:1). Filtration and concentration *in vacuo* furnished 0.78 g (47%) of the title compound as a beige oil.

HRMS *m/z* calcd for $C_{14}H_{17}N_3OS$ $(M)^+$ 275.1092, found 275.1101. Anal. ($C_{14}H_{17}N_3OS$) C, H, N.

EXAMPLE 19

2-(2-Phenoxyethoxy)-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-(2-phenoxyethoxy)pyrazine.

K-*t*-BuO (1.61 g, 14.3 mmol) was added portionwise to a stirred mixture of 2,6-dichloropyrazine (2.03 g, 13.6 mmol) and 2-phenoxyethanol (2.54 g, 18.4 mmol) in dioxane (8 mL) at 0 °C (ice-bath). After 5 min of stirring, the ice-bath was removed and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether, filtered and concentrated *in vacuo*. The oily residue was purified by silica gel chromatography (18 x 5 cm) using *n*-hexane/ethyl acetate (92:8) as eluent.

This furnished 2.92 g (86%) of the title compound as a white solid. HRMS *m/z* calcd for $C_{12}H_{11}ClN_2O_2$ $(M)^+$ 250.0509, found 250.0511. Anal. ($C_{12}H_{11}ClN_2O_2$) C, H, N.

Step 2: 2-(2-Phenoxyethoxy)-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (1.29 g, 5.15 mmol), piperazine (1.30 g, 15.1 mmol) and K_2CO_3 (0.71 g, 5.14 mmol) in acetonitrile (5 mL) was heated in a sealed pyrex flask at 100 °C for 4 h. The reaction mixture was diluted with dichloromethane, filtered, and concentrated *in vacuo*. The light-brown semi-solid residue was purified by silica gel chromatography (15 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. Solvents were evaporated off and the residue was redissolved in ether/$CHCl_3$ (1:1). Filtration and concentration *in vacuo* furnished 1.05 g (68%) of the title compound as a white solid. HRMS *m/z* calcd for $C_{16}H_{20}N_4O_2$ $(M)^+$ 300.1586, found 300.1578. Anal. ($C_{16}H_{20}N_4O_2$) C, H, N.

EXAMPLE 20

2-(Benzyloxy)-6-(1-piperazinyl)pyrazine.*

A mixture of the product from example 13, step 2 (0.73 g, 3.68 mmol), benzyl alcohol (9.4 g, 87 mmol) and K-*t*-BuO was stirred at 125 °C for 4.5 h. The reaction mixture was purified by silica gel chromatography (13 x 5 cm) using $CHCl_3$/MeOH (7:3 followed by 9:1) as eluent. Solvents were evaporated off and the residue was redissolved in ethyl acetate. Filtration and concentration *in vacuo* furnished 0.90 g (90%) of the title compound as a beige oil. HRMS *m/z* calcd for $C_{15}H_{18}N_4O$ $(M)^+$ 270.1481, found 270.1482. Anal. ($C_{15}H_{18}N_4O$) C, H, N. *This compound was also characterized as its maleate salt: mp 155-156 °C. HRMS *m/z* calcd for $C_{15}H_{18}N_4O$ $(M)^+$ 270.1481, found 270.1482. Anal. ($C_{15}H_{18}N_4O \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 21

2-Phenoxy-6-(1-piperazinyl)pyrazine.

A mixture of the product obtained in example 13, step 2 (1.97 g, 9.92 mmol), phenol (2.43 g, 25.8 mmol), CuO (1.0 g, 12.6 mmol), and K_2CO_3 (1.43 g, 10.3 mmol) in dioxane (2 mL) was stirred for 4.5 h at 165 °C in a sealed pyrex tube. The reaction mixture was diluted with $CHCl_3$ and filtered through a pad of Celite. The pad was washed with several portions of $CHCl_3$/MeOH (95:5). Solvent removal *in vacuo* furnished a dark brown oil which was purified by column chromatography on silica gel (14 x 5 cm) using $CHCl_3$/MeOH (95:5, followed by 90:10) as eluent. The brown

oil (1.66 g) was subjected to repeated column chromatography, first on silica gel (18 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent and finally on alumina (4 x 5 cm) using ether/MeOH (95:5) as eluent. This furnished 1.37 g (54%) of the title compound as a light beige oil. HRMS *m/z* calcd for $C_{14}H_{16}N_4O$ $(M)^+$ 256.1324, found 256.1321. Anal. ($C_{14}H_{16}N_4O$) C, H, N.

EXAMPLE 22

2-(1-Phenylethoxy)-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-(1-phenylethoxy)pyrazine.

K-*t*-BuO (2.1 g, 18.7 mmol) was added to a stirred solution of 1-phenyl-1-ethanol (2.45 g, 20.1 mmol) in dioxane (30 mL) at 0 °C (icc-bath). After 10 min of stirring, 2,6-dichloropyrazine (2.49 g, 16.7 mmol) was added whereupon the reaction mixture turned orange colored. After being stirred for a further 1.5 h, ether was added and the mixture was filtered. Concentration in vacuo furnished an orange colored oil that was purified by silica gel chromatography (15 x 5 cm) using *n*-hexane ethyl acetate (9:1) as eluent. This gave 3.29 g (84%) of the title compound as a colorless oil. HRMS *m/z* calcd for $C_{12}H_{11}ClN_2O$ $(M)^+$ 234.0560, found 234.0551.

Step 2: 2-(1-Phenylethoxy)-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (1.53 g, 6.5 mmol), piperazine (1.62 g, 18.9 mmol) and K_2CO_3 (0.90 g, 6.5 mmol) in acetonitrile (6 mL) was heated in a sealed pyrex flask at 90 °C for 3.5 h. The reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The semi-solid residue was purified by silica gel chromatography (13 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. Solvents were evaporated off and the remaining oil was redissolved in $CHCl_3$, filtered through a short plug of alumina and concentrated *in vacuo*. This gave 1.34 g (72%) of the title compound as an oil that solidified when refrigerated. HRMS *m/z* calcd for $C_{16}H_{20}N_4O$ $(M)^+$ 284.1637, found 284.1650. Anal. ($C_{16}H_{20}N_4O \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 23

2-(2-Fluoroethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

Step 1: 2-Chloro-6-(2-fluoroethoxy)pyrazine.

K-*t*-BuO (1.32 g, 11.8 mmol) was added portionwise to a stirred mixture of 2-fluoroethanol (2.16 g, 33.7 mmol) and 2,6-dichloropyrazine (1.61 g, 10.8 mmol) in dioxane (2 mL) at 0 °C (ice-bath). The reaction mixture was then stirred at room temperature for 1 hour, diluted with dichloromethane, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (19 x 4 cm) using *n*-hexane/ethyl acetate (85:15) as eluent. This furnished 1.49 g (78%) of the title compound as a beige liquid. Anal. ($C_6H_6FClN_2O$) C, H, N.

Step 2: 2-(2-Fluoroethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

A mixture of the product from step 1 above (0.94 g, 5.31 mmol), piperazine (1.40 g, 16.3 mmol) and K_2CO_3 (0.81 g, 5.9 mmol) in acetonitrile (5 mL) was stirred at room temperature for 8.5 h and at 65 °C for 4 h. The reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The semi-solid residue was purified by silica gel chromatography (17 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. Solvents were evaporated off and the remaining oil (0.73 g) was redissolved in ether/$CHCl_3$ (1:1) and filtered through a short (4 cm) plug of alumina using ether/MeOH (96:4) as eluent. Solvents were evaporated off and the residue was redissolved in ether and K_2CO_3 was added. Filtration and concentration *in vacuo* furnished 0.57 g (47%) of the free base of the title compound as an oil which was converted into its maleate salt. Recrystallization from MeOH/ether furnished 0.58 g of the title compound as a white powder. Anal. ($C_{10}H_{15}FN_4O \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 24

2-(Cyclopentylmethoxy)-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-(cyclopentylmethoxy)pyrazine.

K-*t*-BuO (1.65 g, 14.7 mmol) was added portionwise to a stirred mixture of cyclopentanemethanol (2.99 g, 29.9 mmol) and 2,6-dichloropyrazine (1.90 g, 12.8 mmol) in dioxane (6 mL) at 0 °C (ice-bath). The reaction mixture was then stirred for 2.5 h, while the temperature was allowed to reach room temperature. The reaction mixture was diluted with dichloromethane/ether (1:1), filtered, and concentated *in*

vacuo. The beige liquid was purified by column chromatography on silica gel (18 x 4 cm) using *n*-hexane/ethyl acetate (94:6) as eluent. Two chromatographic runs afforded 1.66 g (61%) of the title compound as a colorless oil. HRMS *m/z* calcd for $C_{10}H_{13}ClN_2O$ $(M)^+$ 212.0716, found 212.0723. Anal. ($C_{10}H_{13}ClN_2O$) C, H, N.

Step 2: 2-(Cyclopentylmethoxy)-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (1.12 g, 5.27 mmol), piperazine (1.36 g, 15.8 mmol) and K_2CO_3 (0.77 g, 5.6 mmol) in acetonitrile (5 mL) was stirred at 100 °C for 4.5 h in a sealed pyrex flask. The reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The semi-solid residue was purified by silica gel chromatography (15 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. Solvents were evaporated off and the remaining thick oil was redissolved in ether. Filtration and concentration *in vacuo* furnished 1.02 g (74%) of the title compound as a beige oil. HRMS *m/z* calcd for $C_{14}H_{22}N_4O$ $(M)^+$ 262.1794, found 262.1800. Anal. ($C_{14}H_{22}N_4O$) C, H, N.

EXAMPLE 25

2-Benzyl-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-benzylpyrazine

The title compound was prepared in a 20 mmol-scale according to the procedure described in WO 94/26715 with a slight modification. The reaction was carried out at 50 °C for 8 h followed by 10 h at room temperature. Yield: 0.75 g (18%). HRMS *m/z* calcd for $C_{11}H_9ClN_2$ $(M)^+$ 204.0454, found 204.0450.

Step 2: 2-Benzyl-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (0.83 g, 4.0 mmol), piperazine (1.1 g, 12.8 mmol) and K_2CO_3 (0.62 g, 4.49 mmol) in acetonitrile (7 mL) was stirred at 85 °C for 8.5 h. Thr reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The semi-solid residue was purified by silica gel chromatography (20 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. The resulting oil was redissolved in $CHCl_3$ and filtered through a short (4 cm) plug of alumina using

ether/MeOH (96:4) as eluent. Solvent removal *in vacuo* furnished 0.59 g (57%) of the title compound as an oil which became semi-solid upon refrigeration. HRMS *m/z* calcd for $C_{15}H_{18}N_4$ $(M)^+$ 254.1531, found 254.1527. Anal. ($C_{15}H_{18}N_4$) C, H, N.

EXAMPLE 26

2-(3,4-Dihydro-2*H*-chromen-4-yloxy)-6-(1-piperazinyl)pyrazine, Maleate.

Step 1: 2-Chloro-6-(3,4-dihydro-2*H*-chromen-4-yloxy)pyrazine.

K-*t*-BuO (1.28 g, 11.42 mmol) was added to a stirred solution of 4-chromanol (1.81 g, 12.0 mmol) in dioxane (30 mL) at 0 °C (ice-bath). After being stirred for 5 min at room temperature, the mixture was chilled to 0 °C (ice-bath) and 2,6-dichloropyrazine (1.49 g, 10.0 mmol) was added. The reaction mixture was stirred at room temperature for 15 min and diluted with dichloromethane. Filtration and concentration *in vacuo* furnished

an orange thick oil which was purified by chromatography on silica gel (15 x 4 cm) using *n*-hexane/ethyl acetate (8:2) as eluent. This furnished 1.87 g (71%) of the title compound as a colorless oil. HRMS *m/z* calcd for $C_{13}H_{11}ClN_2O_2$ $(M)^+$ 262.0509, found 262.0520. Anal. ($C_{13}H_{11}ClN_2O_2$) C, H, N.

Step 2: 2-(3,4-Dihydro-2*H*-chromen-4-yloxy)-6-(1-piperazinyl)pyrazine, Maleate.

A mixture of the product from step 1 above (1.53 g, 5.81 mmol), piperazine (1.45 g, 16.9 mmol) and K_2CO_3 (0.80 g, 5.81 mmol) in acetonitrile (10 mL) was heated in a sealed pyrex flask at 110 °C for 6.5 h. The reaction mixture was diluted with $CHCl_3$, filtered and concentrated *in vacuo*. The semi-solid residue was purified by column chromatography on silica (13 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. The free base of the title compound was obtained as a viscous oil (1.76 g, 97%) which was converted to its maleate salt. Recrystallization from MeOH/ether furnished 1.78 g (74%) of the title compound as a light yellow powder: mp 179.5-182 °C. HRMS *m/z* calcd for $C_{17}H_{20}N_4O_2$ $(M)^+$ 312.1586, found 312.1581. Anal. ($C_{17}H_{20}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 27

2-[2-(4-Dimethylaminophenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

Step 1: 2-Chloro-6-[2-(4-dimethylaminophenyl)ethoxy]pyrazine.

K-*t*-BuO (2.27 g, 20.3 mmol) was added to a stirred solution of 4-(dimethylamino)phenethyl alcohol (3.55 g, 21.5 mmol) in dioxane (35 mL) at 0 °C (ice-bath). After being stirred for 5 min at 0 °C and 12 min at room temperature, the mixture was chilled to 0 °C (ice-bath) and 2,6-dichloropyrazine (2.62 g, 17.6 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 20 min and diluted with dichloromethane/ether (1:1). Filtration through a pad of Celite, covered with K_2CO_3, and concentration *in vacuo* furnished a yellow oil. This material was purified by chromatography on silica gel (15 x 5 cm) using *n*-hexane/ethyl acetate (85:15). A second chromatograhic run on silica gel (14 x 5 cm) using *n*-hexane/ethyl acetate (88:12) furnished 3.91 g (80%) of the title compound as a colorless oil. Anal. ($C_{14}H_{16}ClN_3O$) C, H, N.

Step 2: 2-[2-(4-Dimethylaminophenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

A mixture of the product from step 1 above (1.83 g, 6.59 mmol), piperazine (1.69 g, 19,6 mmol) and K_2CO_3 (0.92 g, 6.7 mmol) in acetonitrile (25 mL) was heated under reflux for 8.5 h. The reaction mixture was diluted with dichloromethane, filtered through a pad of Celite, and concentrated *in vacuo*. The semi-solid residue was purified by column chromatography on silica (13 x 4 cm) using $CHCl_3$/MeOH (92:8) as eluent. The free base of the title compound was obtained as a beige viscous oil (1.17 g, 54%) which was converted into its maleate salt. Recrystallization from MeOH/ether furnished 1.33 g of the title compound as a light yellow powder. HRMS *m/z* calcd for $C_{18}H_{25}N_5O$ $(M)^+$ 327.2059, found 327.2066. Anal. ($C_{18}H_{25}N_5O \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 28

2-[2-(1*H*-Indol-1-yl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

Step 1: 2-(1*H*-Indol-1-yl)ethanol.*

A mixture of indole (5.71 g, 48.7 mmol), ethylene carbonate (4.72 g, 53.6 mmol) and K_2CO_3 (6.73 g, 48.7 mmol) in DMF (20 mL) was heated under reflux for 2 h. The reaction mixture was diluted with dichloromethane, filtered, and concentrated *in vacuo*.

The light brown oily residue was purified by chromatography on silica gel (13 x 6 cm)
using *n*-hexane/ethyl acetate (1:1) as eluent. This gave 1.78 g (23%) of the title compound as a beige oil. HRMS *m/z* calcd for $C_{10}H_{11}NO$ $(M)^+$ 161.0841, found 161.0849. Anal. ($C_{10}H_{11}NO \cdot 0.1H_2O$) C, H, N. *Previously described in a) J. Med. Chem. 1992, 35, 994-1001; b) *ibid.* 1998, 41, 1619-1630.

Step 2: 2-Chloro-6-[2-(1*H*-indol-1-yl)ethoxy]pyrazine.
K-*t*-BuO (0.67 g, 5.93 mmol) was added to a stirred solution of the product obtained in step 1 above (0.67 g, 5.93 mmol) in dioxane (20 mL) at 0 °C (ice-bath). After being stirred for 7 min at 0 °C and 5 min at room temperature, the mixture was chilled to 0 °C (ice-bath) and 2,6-dichloropyrazine (2.62 g, 17.6 mmol) was added. The yellowish reaction mixture was stirred at 0 °C for 20 min and at room temperature for 10 min and then diluted with dichloromethane. Drying (K_2CO_3), filtration, and concentration *in vacuo* furnished a beige oil. This material was purified by chromatography on silica gel (13 x 4 cm) using *n*-hexane/ethyl acetate (80:20). This furnished 1.39 g (94%) of the title compound as an oil that solidified upon standing. HRMS *m/z* calcd for $C_{14}H_{12}ClN_3O$ $(M)^+$ 273.0669, found 273.0671. Anal. ($C_{14}H_{12}ClN_3O$) C, H, N.

Step 3: 2-[2-(1*H*-Indol-1-yl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.
A mixture of the product from step 1 above (1.05 g, 3.84 mmol), piperazine (0.96 g, 11.1 mmol) and K_2CO_3 (0.53 g, 3.84 mmol) was heated at 85 °C for 7 h. The reaction mixture was diluted with $CHCl_3$, filtered, and concentrated *in vacuo*. The semi-solid residue was purified by chromatography on silica gel (11 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. The resulting oil was redissolved in $CHCl_3$ and filtered through a short (4 cm) plug of alumina covered by K_2CO_3 using $CHCl_3$ as

eluent. Solvent removal *in vacuo* furnished 1.02 g (82%) of the free base of the title compound as a beige oil which was converted into its maleate. Recrystallization from MeOH/ether furnished 1.00 g (75%) of the title compound as a light yellow powder: mp 160.5-163 °C. HRMS *m/z* calcd for $C_{18}H_{21}N_5O$ $(M)^+$ 323.1746, found 323.1757. Anal. ($C_{18}H_{21}N_5O \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 29

2-[2-(1*H*-Indol-3-yl)ethoxy]-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-[2-(1*H*-indol-3-yl)ethoxy]pyrazine.

K-*t*-BuO (2.32 g, 20.6 mmol) was added to a stirred solution of tryptophol (1.7 g, 10.6 mmol) in dioxane (30 mL) at 0 °C (ice-bath). After being stirred for 10 min at 0 °C and 10 min at room temperature, the mixture was chilled to 0 °C (ice-bath) and 2,6-dichloropyrazine (1.37 g, 9.17 mmol) was added. The yellowish reaction mixture was stirred at 0 °C for 30 min and for a further 20 min at room temperature. The mixture was diluted with dichloromethane, filtered, and concentrated *in vacuo* to furnish a brownish oil. This material was purified by chromatography on silica gel (14 x 5 cm) using *n*-hexane/ethyl acetate (75:25). This furnished 1.38 g (55%) of the title compound as a beige solid. Purity >90% by ^{1}H NMR in $CDCl_3$.

Step 2: 2-[2-(1*H*-Indol-3-yl)ethoxy]-6-(1-piperazinyl)pyrazine.

A mixture of the product from Step 1 above (1.07 g, 3.90 mmol), piperazine (0.98 g, 11.3 mmol) and K_2CO_3 (0.54 g, 3.9 mmol) in acetonitrile (11 mL) was heated at 85 °C for 5 h and at 110 °C for 8 h in a sealed pyrex flask. The reaction mixture was diluted with $CHCl_3$, filtered, and concentrated *in vacuo*. The semi-solid residue was purified by chromatography on silica gel (11 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. The resulting oil was redissolved in $CHCl_3$ and filtered through a short plug of alumina, covered by K_2CO_3, using $CHCl_3$ as eluent. Solvent removal *in vacuo* furnished 0.50 g (23%) of the title compound as an oil that solidified upon standing: mp 133-135 °C. HRMS *m/z* calcd for $C_{18}H_{21}N_5O$ $(M)^+$ 323.1746, found 323.1763. Anal. ($C_{18}H_{21}N_5O$)

C, H, N.

EXAMPLE 30

4-[(4-Fluorobenzyl)oxy]-2-(1-piperazinyl)pyrimidine, Dihydrochloride.

K-*t*-BuO (0.224 g, 2.00 mmol) was added to a solution of 4-fluorobenzyl alcohol (0.252 g, 2.00 mmol) in *tert*-butanol (5.4 mL). After being stirred for 30 min at room temperature, 2,4-dichloryrimidine (0.298 g, 2.00 mmol) in *tert*-butanol (2 mL) was added. The reaction mixture was stirred over night, poured into 5% aqueous NaOH and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. A solution of piperazine (0.516 g, 6.00 mmol) in THF (5 mL) was added and the resulting mixture was stirred over night. The reaction mixture was concentrated and purified by chromatography on silica using dichloromethane/MeOH (1% HCl) (using gradient 99:1 to 9:1) to give 0.24 g (33%) of the title compound. MS *m/z* 288 $(M)^+$ and 5 fragments supporting the stated structure. HRMS *m/z* calcd for $C_{15}H_{17}FN_4O$ $(M)^+$ 288.1386, found 288.1378.

EXAMPLE 31

4-[(2-Methoxybenzyl)oxy]-2-(1-piperazinyl)pyrimidine, Dihydrochloride.

The title compound was prepared according to the procedure of example 30 starting from 2-methoxybenzyl alcohol (0.28 g, 2.0 mmol) to give 0.30 g (40%) of the title compound. MS *m/z* 300 $(M)^+$ and 3 fragments supporting the stated structure. HRMS *m/z* calcd for $C_{16}H_{20}N_4O_2$ $(M)^+$ 300.1586, found 300.1586.

EXAMPLE 32

4-(Benzyloxy)-2-(1-piperazinyl)pyrimidine, Dihydrochloride.

The title compound was prepared according to the procedure of example 30 starting from benzyl alcohol (0.22 g, 2.0 mmol) to give 0.23 g (31%) of the title compound. MS m/z 270 $(M)^+$ and 6 fragments supporting the stated structure. HRMS *m/z* calcd for $C_{15}H_{18}N_4O$ $(M)^+$ 270.1481, found 270.1488.

EXAMPLE 33

4-(1-Piperazinyl)-2-{[3-(trifluoromethoxy)benzyl]oxy}pyrimidine, Trifluoroacetate.

Step 1: 2-Chloro-4-[1-(4-*tert*-butoxycarbonyl)piperazinyl]pyrimidine.*

1-*tert*-Butoxycarbonylpiperazine (3.72 g, 0.02 mol) was added to a stirred solution of 2,4-dichloropyrimidine (2.98 g, 0.02 mol) and diisopropylethylamine (2.58 g, 0.02 mol) in dichloromethane (200 mL). The reaction mixture was stirred at ambient temperature for 48 h and then concentrated under reduced pressure. The residue obtained was flash-chromatographed over silica using dichloromethane/ether (4:1) as eluent to afford 3.44 g (58%) of the title compound as a colourless solid whose NMR and MS spectra were in agreement with the expected structure. MS *(ES+) m/z* 299 and 301 $(M+H)^+$. *Previously described in WO 9911657.

Step 2: 2-Chloro-4-(1-piperazinyl)pyrimidine.*

2-Chloro-4-[1-(4-*tert*-butoxycarbonyl)piperazinyl]pyrimidine. (2.00 g, 6.7 mmol; obtained in step 1 above) was dissolved in a 25% v/v solution of trifluoroacetic acid in dichloromethane (25 mL). The solution was stirred at room temperature for 40 min then the solvent was removed by evaporation under reduced pressure. The oily residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic extract was dried and evaporated under reduced pressure to afford 1.04 g (79%) of the title compound as a colourless solid whose NMR and MS spectra were in agreement with the expected structure. MS *(ES+) m/z* 199 and 301 $(M+H)^+$. *Previously described in WO 9535293.

Step 3: 4-(1-Piperazinyl)-2-{[3-(trifluoromethoxy)benzyl]oxy}pyrimidine, Trifluoroacetate.

A solution of 2-chloro-4-(1-piperazinyl)pyrimidine (0.04 g, 0.2 mmol; obtained in Step 2 above) and 3-trifluoromethoxybenzyl alcohol (0.077 g, 0.4 mmol) in tetrahydrofuran (4.0 ml) was treated with a solution of K-*t*-BuO in *tert*-butanol (1M; 0.4 mL, 0.4 mmol). The resulting mixture was heated at 70 °C overnight then allowed to cool. The solvent was evaporated under reduced pressure then the crude reaction mixture partitioned between ethyl acetate (4.0 mL) and water (2.0 mL). The organic phase was evaporated then purified by preparative C-18 HPLC using CH_3CN/H_2O/TFA (gradient: CH_3CN 20% to 97%, TFA 0.1%) to afford 11 mg (12%) of the title compound. Purity 85% (HPLC). MS *(ES+) m/z* 355 $(M+H)^+$.

EXAMPLE 34

2-[(3-Methoxybenzyl)oxy]-4-(1-piperazinyl)pyrimidine, Trifluoroacetate.

The title compound was prepared according to the procedure of example 33, step 3 starting from 3-methoxybenzyl alcohol (0.055 g, 0.40 mmol) to give 5 mg (6%) of the expected product. Purity >90% (HPLC). MS *(ES+) m/z* 301 $(M+H)^+$.

EXAMPLE 35

2-{[3-(Benzyloxy)benzyl]oxy}-4-(1-piperazinyl)pyrimidine, Trifluoroacetate.

The title compound was prepared according to the procedure of example 33, step 3 starting from 3-benzyloxybenzyl alcohol (0.086 g, 0.40 mmol) to give 10 mg (10%) of the expected product. Purity >90% (HPLC). MS *(ES+) m/z* 377 $(M+H)^+$.

EXAMPLE 36

2-[(3-Phenoxybenzyl)oxy]-4-(1-piperazinyl)pyrimidine, Trifluoroacetate.

The title compound was prepared according to the procedure of example 33, step 3 starting from 3-phenoxybenzyl alcohol (0.08 g, 0.4 mmol) to give 8 mg (8%) of the expected product. Purity > 90% (HPLC). MS *(ES+) m/z* 363 $(M+H)^+$.

EXAMPLE 37

2-(2-Naphthylmethoxy)-4-(1-piperazinyl)pyrimidine, Trifluoroacetate.

The title compound was prepared according to the procedure of example 33, step 3 starting from 2-naphthylmethyl alcohol (0.063 g, 0.4 mmol) to give 10 mg (12%) of the expected product. Purity >90% (HPLC). MS *(ES+) m/z* 321 $(M+H)^+$.

EXAMPLE 38

4-(1-Piperazinyl)-2-{[3-(2-Trifluoromethyl)benzyl]oxy}pyrimidine, Trifluoroacetate.

A solution of. 2-chloro-4-[1-(4-*tert*-butoxycarbonyl)piperazinyl]pyrimidine (obtained in example 33, step 1; 0.04 g, 0.2 mmol) and 2-trifluoromethylbenzyl alcohol (0.035 g, 0.20 mmol) in tetrahydrofuran (2.0 mL) was treated with K-*t*-BuO in *tert*-butanol (1M; 0.2 mL, 0.2 mmol). The resulting mixture was heated at 65 °C overnight then

allowed to cool. The solvent was evaporated under reduced pressure then the crude reaction mixtures partitioned between ethyl acetate (4.0 mL) and water (2.0 mL). The organic phase was evaporated then purified by preparative C-18 HPLC using CH_3CN/H_2O/TFA (gradient: CH_3CN 20% to 97%, TFA 0.1%) to afford the BOC protected product. This material was then dissolved in a 25% (v/v) solution of trifluoroacetic acid in dichloromethane (5.0 mL) and allowed to stand at room temperature for 30 min. Removal of the solvent under reduced pressure gave 40 mg (44 %) of the title compound. Purity >90% (HPLC). MS *(ES+) m/z* 339 $(M+H)^+$.

EXAMPLE 39

(2*S*)-1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine.

Step 1: (3*S*)-3-Methyl-1-tritylpiperazine.

To a solution of 2-(*S*)-methylpiperazine (2.62 g, 26.2 mmol) in dichloromethane (100 mL) was trityl chloride (7.30 g, 26.2 mmol) added and the mixture was stirred at ambient temperature for 1.5 h. The organic phase was washed (x 1) with 1 M aqueous K_2CO_3, water, and brine. Drying ($MgSO_4$) and solvent removal *in vacuo* furnished a quantitative yield of the title compound as a glassy oil which solidified upon standing. This material was used directly in the next step.

Step 2: (2*S*)-1-(6-Chloro-2-pyrazinyl)-2-methylpiperazine.

A mixture of 2-6-dichloropyrazine (1.10 g, 7.39 mmol), and the product from step 1 above (2.30 g, 6.72 mmol) and K_2CO_3 (1.0 g, 7.39 mmol) in dry DMF (40 mL) was stirred at 110 °C over night. The dark reaction mixture was filtered through a plug of silica and the solvent was removed under reduced pressure. The remaining oil was dissolved in $CHCl_3$/*n*-heptane (1:1) and filtered through a second plug of silica. The solvent was evaporated and the remaining yellow oil was suspended in EtOH (80 mL).

4 M aqueous HCl (2 mL) was added and the mixture was ultrasonicated for 20 min. The solvent was evaporated and the remaining oil was taken up between water/$CHCl_3$. The organic phase was made alkaline (11 M aqueous NaOH) and extracted twice with $CHCl_3$. The combined dried ($MgSO_4$) organic layers were concentrated *in vacuo* to afford 0.75 g (54%) of the title compound as a yellow oil.

MS *m/z* 212/214 $(M)^+$ ($^{35}Cl/^{37}Cl$-isotope pattern). HRMS *m/z* calcd for $C_9H_{13}ClN_4$ $(M)^+$ 212.0829, found 212.0827.

Step 3: (2*S*)-1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine, Acetate.

To a solution of (2*S*)-1-(6-chloro-2-pyrazinyl)-2-methylpiperazine (prepared in step 2 above; 0.16 g, 0.72 mmol) and benzyl alcohol (0.12 g, 1.1 mmol) in DMF (4 mL) was Na-*t*-BuO (0.14 g, 1.4 mmol) added and the mixture was stirred at 150 °C overnight. The solvent was evaporated off under reduced pressure and the residue taken up between $CHCl_3/H_2O$. The organic phase was concentrated and the crude product was purified by preparative C18-HPLC using acetonitrile/H_2O/HOAc with UV detection at 254 nm. Yield: 1 mg (0.4%). MS *m/z* 284 $(M)^+$. HRMS *m/z* calcd for $C_{16}H_{20}N_4O$ $(M)^+$ 284.1637, found 284.1640.

EXAMPLE 40

(2*S*)-1-[6-(Benzyloxy)-4-(trifluoromethyl)-2-pyridinyl]-2-methylpiperazine, Acetate.

Step 1: (2*S*)-1-[6-Chloro-4-(trifluoromethyl)-2-pyridinyl]-2-methylpiperazine.

The title compound, obtained as an oil, was prepared from the product of example 39, step 1 (2.62 g, 7.62 mmol) and 2,6-dichloro-4-trifluoromethylpyridine (1.81 g, 8.38 mmol) according to the procedure of example 39, step 2. Yield: 0.24 g (11%). MS *m/z* 279/281 $(M)^+$ ($^{35}Cl/^{37}Cl$-isotope pattern). HRMS *m/z* calcd for $C_{11}H_{13}ClF_3N_3$ $(M)^+$ 279.0750, found 279.0751.

Step 2: (2*S*)-1-[6-(Benzyloxy)-4-(trifluoromethyl)-2-pyridinyl]-2-methylpiperazine, Acetate.

The title compund was prepared from the product of step 1 above (0.24 g, 0.86 mmol), benzyl alcohol (0.14 g, 1.29 mmol) and Na-*t*-BuO (0.165 g, 1.72 mmol) according to the procedure of example 39, step 3. MS *m/z* 351 $(M)^+$. HRMS *m/z* calcd for $C_{18}H_{20}F_3N_3O$ $(M)^+$ 351.1558, found 351.1555.

EXAMPLE 41

1-[6-(Benzyloxy)-2-pyrazinyl]-2-ethylpiperazine, Acetate.

Step 1: 1-Benzyl-3-ethylpiperazine.*

Benzyl bromide (38.7 g, 0.22 mol) was added in portions to a chilled (~ 0 °C) solution of 2-ethylpiperazine (25 g, 0.22 mol) in DMF (150 mL) with such a rate that the temperature did not exceed 20 °C. The mixture was stirred for 1 h, the solvent was evaporated and the residue was partitioned between $CHCl_3$/0.5 M aqueous HCl. The aqueous phase was made alkaline (11 M NaOH) and extracted three times with $CHCl_3$. The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography on silica using $CHCl_3$, followed by $CHCl_3$/MeOH/NH_4OH (95:5:0.3) as eluents to give 31.6 g (70%) of the title compound as a yellowish oil. Anal. ($C_{13}H_{20}N_2$) H, N; C: calcd, 76.42; found, 75.85. *Described in WO 00/76984.

Step 2: 4-Benzyl-1-(6-chloro-2-pyrazinyl)-2-ethylpiperazine.

The title compound was prepared according to the procedure of example 39, step 2, starting from the product obtained in step 1 above (4.60 g, 22.5 mmol), 2,6-dichloropyrazine (3.90 g, 26.2 mmol) and K_2CO_3 (6.22 g, 45.0 mmol). Yield: 6.15 g (86%). MS *m/z* 316/318 $(M)^+$ ($^{35}Cl/^{37}Cl$-isotope pattern). HRMS *m/z* calcd for $C_{17}H_{21}ClN_4$ $(M)^+$ 316.1455, found 316.1455.

Step 3: 1-(6-Chloro-2-pyrazinyl)-2-ethylpiperazine.

1-Choroethyl chloroformate (4.16 g, 29.1 mmol) was added dropwise under 2 h to a stirred solution of the product obtained in step 2 above (6.15 g, 19.4 mmol) in dry dichloromethane (75 mL) at 0 °C. After being stirred at room temperature for 15 h, the reaction mixture was concentrated *in vacuo* and methanol was added. The mixture was heated at reflux for 2 h and concentrated. The residue was dissolved in $CHCl_3$ and passed through a short (4 cm) plug of silica gel using $CHCl_3$/MeOH (8:2) as eluent. Solvents were evaporated off and the residue was purified by chromatography on silica gel (12 x 5 cm) using $CHCl_3$/MeOH/Et_3N (95:5:0.2) as eluent. This provided 1.9 g (43%) of the title compound as an oil. MS *m/z* 226/228 $(M)^+$ ($^{35}Cl/^{37}Cl$-isotope pattern). HRMS *m/z* calcd for $C_{10}H_{15}ClN_4$ $(M)^+$ 226.0985, found 226.0986.

Step 4: 1-[6-(Benzyloxy)-2-pyrazinyl]-2-ethylpiperazine, Acetate.

The title compund was prepared according to the procedure of example 39, step 3, starting from the product of step 3 above (0.163 g, 0.72 mmol), benzyl alcohol (0.12 g, 1.08 mmol) and Na-*t*-BuO (0.14 g, 1.4 mmol). Purity 90% (HPLC). MS *m/z* 298 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{22}N_4O$ $(M)^+$ 298.1794, found 298.1802.

EXAMPLE 42

2-[(4-Fluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine.

4-Fluorobenzyl alcohol (0.189 g, 1.50 mmol) was dissolved in THF (1 mL) and treated with NaH (0.065 g, 55% dispersion in mineral oil, 1.5 mmol). The reaction mixture was stirred at room temperature for 3 h. A solution of 2,6-dichloropyrazine (1.57 g, 10.5 mmol) in THF (7 mL) was added and the resulting mixture was stirred for 4 h at room temperature. Piperazine (0.580 g, 6.75 mmol) and K_2CO_3 (0.43 g, 4.5 mmol) were added and the mixture was stired at 60 °C over night. Filtration, concentration, and purification by chromatography on silica gel using ethyl acetate/acetic acid/methanol/water (24:3:3:2) as eluent furnished 0.20 g (46%) of the title compound as a white solid: mp 183 °C. HRMS *m/z* calcd for $C_{15}H_{17}FN_4O$ $(M)^+$ 288.1386, found 288.1380. Anal. ($C_{15}H_{17}FN_4O \cdot 2.6H_2O$) C, H, N.

EXAMPLE 43

2-[(4-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetate.

The title compound was prepared according to the procedure of example 42 starting from 4-methoxybenzyl alcohol (0.207 g, 1.50 mmol) and was isolated as a yellow solid. Yield: 0.79 g (67%). HRMS *m/z* calcd for $C_{16}H_{20}N_4O_2$ $(M)^+$ 300.1586, found 300.1584.

EXAMPLE 44

2-[2-(4-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine, 0.5 Acetate.

The title compound was prepared according to the procedure of example 42 starting from 2-(4-fluorophenyl)ethanol (0.210 g, 1.50 mmol) and was isolated as a yellow

solid. Yield: 0.145 g (27%). HRMS *m/z* calcd for $C_{16}H_{19}FN_4O$ $(M)^+$ 302.1543, found 302.1554. Anal. ($C_{16}H_{19}FN_4O \cdot 0.5CH_3COOH \cdot H_2O$) C, H, N.

EXAMPLE 45

2-[2-(3-Methoxyphenyl)ethoxy]-6-(4-piperidinyloxy)pyrazine.

Step 1: *tert*-Butyl 4-[(6-chloro-2-pyrazinyl)oxy]-1-piperidinecarboxylate.

A mixture of 2,6-dichloropyrazine (5.00 g, 33.6 mmol), *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (6.76 g, 33.6 mmol) and K-*t*-BuO (1 M in *tert*-butanol; 35 mL, 35 mmol) in Et_3N (200 mL) was stirred at room temperature for 12 h. The reaction was quenched with water (50 mL) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated aqueous KH_2PO_4, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was recrystallized from ethanol/water to give 9.50 g (90 %) of the title compound as a white solid: mp 86-87 °C; MS *m/z* 313 $(M)^+$. Anal. ($C_{14}H_{20}ClN_3O_3$) C, H, N.

Step 2: 2-Chloro-6-(4-piperidinyloxy)pyrazine.

Aqueous 3.0 M HCl (12 mL) was added to a solution of the product obtained in Step 1 above (5.00 g, 15.9 mmol) in methanol (200 mL). The reaction mixture was stirred at 50 °C for 5 h and concentrated *in vacuo*. The residue was dissolved in water (50 mL) and basified with K_3PO_4. The aqueous phase was extracted with ethyl acetate (5 x 40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. This gave 3.08 g (91%) of the title compound as a colorless oil which slowly decomposed upon standing. HRMS *m/z* calcd for $C_9H_{12}ClN_3O$ $(M)^+$ 213.0669, found 213.0663.

Step 3: 2-[2-(3-Methoxyphenyl)ethoxy]-6-(4-piperidinyloxy)pyrazine.

A solution of the product obtained in Step 2 above (0.043 g, 0.20 mmol) in DMF (1.1 mL) was added to a mixture of 3-methoxyphenethyl alcohol (0.061 g, 0.40 mmol) and K-*t*-BuO (1.0 M in *tert*-butanol; 0.4 mL, 0.40 mmol) in DMF (0.8 mL). The reaction mixture was vortexed for 16 h at 50 °C under nitrogen, quenched with water (0.1 mL) and concentrated *in vacuo*. The residue was partitioned between water (2 mL) and 4 ethyl acetate (4 mL) and poured through a hydromatrix column, which was eluted with ethyl acetate/Et_3N (95:5). Solvents were evaporated off and the

residue was dissolved in methanol/water (50 mL) and loaded onto a conditioned weak cation exchange SPE column (1 g, Amberlyst CG-50 I). The column was washed with water (10 mL) and methanol (10 mL). The compound was eluted with aqueous 2.0 M NH_3 in methanol (20 m) and concentrated *in vacuo*. The residue was analysed for identity and purity by LC-UV/MS. Yield: 8 mg (12%). HRMS *m/z* calcd for $C_{18}H_{23}N_3O_3$ $(M)^+$ 329.1739, found 329.1743.

EXAMPLE 46

2-(2-Phenylethoxy)-6-(4-piperidinyloxy)pyrazine.

The title compound was prepared according the procedure of example 45, step 3, starting from 2-phenylethanol (49 mg, 0.40 mmol). The product was analysed for identity and purity by LC-UV/MS. Yield: 7 mg (12%). HRMS *m/z* calcd for $C_{17}H_{21}N_3O_2$ $(M)^+$ 299.1634, found 299.1630.

EXAMPLE 47

2-(3-Phenoxypropoxy)-6-(4-piperidinyloxy)pyrazine.

The title compound was prepared according the procedure of example 45, step 3, starting from 3-phenoxy-1-propanol (61 mg, 0.40 mmol). The product was analysed for identity and purity by LC-UV/MS. Yield: 28 mg (43%). HRMS *m/z* calcd for $C_{18}H_{23}N_3O_3$ $(M)^+$ 329.1739, found 329.1743.

EXAMPLE 48

2-[(5-Phenylpentyl)oxy]-6-(4-piperidinyloxy)pyrazine.

The title compound was prepared according the procedure of example 45, step 3, starting from 5-phenyl-1-pentanol (66 mg, 0.40 mmol). The product was analysed for identity and purity by LC-UV/MS. Yield: 17 mg (25%).

EXAMPLE 49

2-{[3-(Benzyloxy)benzyl]oxy}-6-(4-piperidinyloxy)pyrazine.

The title compound was prepared according the procedure of example 45, step 3,

starting from 3-benzyloxybenzyl alcohol (86 mg, 0.40 mmol). The product was analysed for identity and purity by LC-UV/MS. Yield: 43 mg (55%). HRMS *m/z* calcd for $C_{23}H_{25}N_3O_3$ $(M)^+$ 391.1896, found 391.1905.

EXAMPLE 50

2-[1-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine.

Step 1: 2-Chloro-6-[1-(2-methoxyphenyl)ethoxy]pyrazine.

K-*t*-BuO (0.67 g, 5.97 mmol) was added to a stirred solution of 1-(2-methoxyphenyl)ethanol (0.96 g, 6.28 mmol) in dioxane (15 mL) at 0 °C (ice-bath). After 5 min of stirring at room temperature, the reaction mixture was chilled to 0 °C (ice-bath) and 2,6-dichloropyrazine (0.78 g, 5.23 mmol) was added whereupon the reaction mixture turned yellow. After being stirred for 35 min, dichloromethane and K_2CO_3 were added and the mixture was filtered. Concentration *in vacuo* furnished a yellow oil that was purified by silica gel chromatography (15 x 4 cm) using *n*-hexane ethyl acetate (8:2) as eluent. This gave 1.21 g (92%) of the title compound as a colorless oil. HRMS *m/z* calcd for $C_{13}H_{13}ClN_2O_2$ $(M)^+$ 264.0666, found 264.0677. Anal. ($C_{13}H_{13}ClN_2O_2$) C, H, N.

Step 2: 2-[1-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine.

A mixture of the product from step 1 above (0.93 g, 3.53 mmol) piperazine (0.88 g, 10.2 mmol) and K_2CO_3 (0.49 g, 3.53 mmol) in acetonitrile (7 mL) was heated in a sealed pyrex flask at 90 °C for 6.5 h. The reaction mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The semi-solid residue was purified by silica gel chromatography (13 x 4 cm) using $CHCl_3$/MeOH (9:1) as eluent. Solvents were evaporated off and the remaining oil was redissolved in $CHCl_3$, filtered through a short plug of alumina, covered with K_2CO_3, using $CHCl_3$ as eluent. Solvent removal *in vacuo* gave 0.74 g (67%) of the title compound as a beige oil. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_2$ $(M)^+$ 314.1743, found 314.1733. Anal. ($C_{17}H_{22}N_4O_2 \cdot 0.5H_2O$) C, H, N.

EXAMPLE 51

1-[6-(Benzyloxy)-2-pyrazinyl]-*trans*-2,5-dimethylpiperazine.

Step 1: 1-(6-Chloro-2-pyrazinyl)-*trans*-2,5-dimethylpiperazine.

A mixture of 2,6-dichloropyrazine (0.40 g, 2.68 mmol), *trans*-2,5-dimethylpiperazine (0.62 g, 5.43 mmol), K_2CO_3 (0.41 g, 3.0 mmol) in acetonitrile (5 mL) was stirred at 90 °C for 6 h in a sealed pyrex tube. After cooling, the reaction mixture was filtered and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH (9:1) as eluent. This furnished 0.15 g (25%) of the title compound as an oil. HRMS *m/z* calcd for $C_{10}H_{15}ClN_4$ $(M)^+$ 226.0985, found 226.0983.

Step 2: 1-[6-(Benzyloxy)-2-pyrazinyl]-*trans*-2,5-dimethylpiperazine.

The title compound was prepared according to the procedure of example 20, starting from 1-(6-chloro-2-pyrazinyl)-*trans*-2,5-dimethylpiperazine (1.23 g, 5.40 mmol; obtained in step 1 above), benzyl alcohol (8.36 g, 77.3 mmol), and K-*t*-BuO (1.99 g, 17.7 mmol). The reaction mixture was heated at 95 °C for 5.5 h. The yield of the title compound was 0.47 g (29%) which was obtained as an oil. Purity 99% (HPLC). MS *m/z* 298 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{22}N_4O$ $(M)^+$ 298.1794, found 298.1798.

EXAMPLE 52

2-[2-(2,3-Dimethoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(2,3-dimethoxyphenyl)ethoxy]pyrazine [0.65 g, 2.2 mmol; obtained according to the procedure of example 50, step 1, starting from 2-(2,3-dimethoxyphenyl)ethan-1-ol], piperazine (0.57 g, 6.7 mmol) and K_2CO_3 (0.31 g, 2.22 mmol). The free base of the title compound was converted into its maleate salt. Recrystallization from MeOH-ether furnished 0.45 g (44%) of the title compound. Purity 98% (HPLC). MS *m/z* 345 $(M + H)^+$. HRMS *m/z* calcd for $C_{18}H_{24}N_4O_3$ $(M)^+$ 344.1848, found 344.1861.

EXAMPLE 53

2-[2-(2-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(2-fluorophenyl)ethoxy]pyrazine (2.76 g, 10.9 mmol; obtained according to the procedure of example 50, step 1, starting from 2-fluorophenethyl alcohol), piperazine (2.91 g, 33.8 mmol) and K_2CO_3 (1.51 g, 10.9 mmol). The yield of the free base of the title compound was 1.88 g (57%) which was converted into its maleate salt. Recrystallization from MeOH-ether furnished 2.11 g of the title compound. Purity 100% (HPLC). MS *m/z* 303 $(M + H)^+$. HRMS *m/z* calcd for $C_{16}H_{19}FN_4O$ $(M)^+$ 302.1543, found 302.1550.

EXAMPLE 54

2-[(2,3-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(2,3-dimethoxybenzyl)oxy]pyrazine (2.51 g, 8.93 mmol; obtained according to the procedure of example 50, step 1, starting from 2,3-dimethoxybenzyl alcohol), piperazine (2.38 g, 27.7 mmol) and K_2CO_3 (1.23 g, 8.9 mmol). The yield of the title compound was 1.66 g (56%) which was obtained as an oil. Purity 100% (HPLC). MS *m/z* 331 $(M + H)^+$. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_3$ $(M)^+$ 330.1692, found 330.1690.

EXAMPLE 55

2-(2,3-Dihydro-1*H*-inden-1-ylmethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(2,3-dihydro-1*H*-inden-1-ylmethoxy)pyrazine (3.22 g, 13.1 mmol; obtained according to the procedure of example 50, step 1, starting from 1-indanol), piperazine (3.49 g, 40.5 mmol) and K_2CO_3 (1.8 g, 13.0 mmol). The yield of the free base of the title compound was 2.19 g (57%) which was obtained as an oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 296 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{20}N_4O$ $(M)^+$ 296.1637, found 296.1643.

EXAMPLE 56

2-(4-Phenoxybutoxy)-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(4-phenoxybutoxy)pyrazine (1.99 g, 7.14 mmol; obtained according to the procedure of example 50, step 1, starting from 4-phenoxy-1-butanol*), piperazine (1.84 g, 21.4 mmol) and K_2CO_3 (0.99 g, 7.14 mmol). The yield of the title compound was 1.52 g (65%) which was obtained as an oil. Purity 100% (HPLC). MS *m/z* 329 $(M + H)^+$. HRMS *m/z* calcd for $C_{18}H_{24}N_4O_2$ $(M)^+$ 328.1899, found 328.1894. *Prepared by reduction ($LiAlH_4$) of the corresponding acid (*cf.* J. Org. Chem. 1965, 30, 2441-2447; *ibid.* 1968, 33, 2271-2284).

EXAMPLE 57

2-[(5-Phenoxypentyl)oxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(5-phenoxypentyl)oxy]pyrazine (2.06 g, 7.03 mmol; obtained according to the procedure of example 50, step 1, starting from 5-phenoxy-1-pentanol*), piperazine (1.88 g, 21.8 mmol) and K_2CO_3 (0.97 g, 7.03 mmol). The yield of the title compound was 1.15 g (48%) which was obtained as a white solid. Purity 100% (HPLC). MS *m/z* 343 $(M + H)^+$. HRMS *m/z* calcd for $C_{19}H_{26}N_4O_2$ $(M)^+$ 342.2056, found 342.2054. *Described in J. Org. Chem. 1968, 33, 2271-2284.

EXAMPLE 58

2-[(2,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(2,5-dimethoxybenzyl)oxy]pyrazine (1.02 g, 3.63 mmol; obtained according to the procedure of example 50, step 1, starting from 2,5-dimethoxybenzyl alcohol), piperazine (0.94 g, 10.9 mmol) and K_2CO_3 (0.50 g, 3.63 mmol). The yield of the title compound was 0.64 g (53%) which was obtained as a beige solid. Purity 100% (HPLC). MS *m/z* 331 $(M + H)^+$. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_3$ $(M)^+$ 330.1692, found 330.1692.

EXAMPLE 59

2-[2-(3,4-Dimethoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(3,4-dimethoxyphenyl)ethoxy]pyrazine [2.13 g, 7.23 mmol; obtained according to the procedure of example 50, step 1, starting from 2-(3,4-dimethoxyphenyl)ethan-1-ol], piperazine (1.93 g, 22.4 mmol) and K_2CO_3 (1.0 g, 7.2 mmol). The yield of the title compound was 1.72 g (69%) which was obtained as a beige oil. Purity 100% (HPLC). MS *m/z* 345 $(M + H)^+$. The free base was converted into ints maleate salt. HRMS *m/z* calcd for $C_{18}H_{24}N_4O_3$ $(M)^+$ 344.1848, found 344.1832.

EXAMPLE 60

2-{[2-(2-Phenylethyl)benzyl]oxy}-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-{[2-(2-phenylethyl)benzyl]oxy}pyrazine (1.72 g, 5.30 mmol; obtained according to the procedure of example 50, step 1, starting from 2-phenethylbenzyl alcohol), piperazine (1.37 g, 16.0 mmol) and K_2CO_3 (0.73 g, 5.3 mmol). The yield of the title compound was 1.38 g (69%) which was obtained as an oil. Purity 100% (HPLC). MS *m/z* 375 $(M + H)^+$. HRMS *m/z* calcd for $C_{23}H_{26}N_4O$ $(M)^+$ 374.2107, found 374.2113.

EXAMPLE 61

2-[(3-Phenoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(3-phenoxybenzyl)oxy]pyrazine (1.99 g, 6.36 mmol; obtained according to the procedure of example 50, step 1, starting from 3-phenoxybenzyl alcohol), piperazine (1.94 g, 22.5 mmol) and K_2CO_3 (0.88 g, 6.4 mmol). The yield of the title compound was 1.58 g (69%) which was obtained as an oil. Purity 100% (HPLC). MS *m/z* 363 $(M + H)^+$. HRMS *m/z* calcd for $C_{21}H_{22}N_4O_2$ $(M)^+$ 362.1743, found 362.1739.

EXAMPLE 62

(2*R*)-1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine, Maleate.

Step 1: (3*R*)-3-Methyl-1-tritylpiperazine.

The title compound was prepared according to the procedure of Example 39, step 1, with the exception that (2*R*)-methylpiperazine was substituted for (2*S*)-methylpiperazine. The title compound was obtained as a light yellow crispy solid.

Step 2: (2*R*)-1-(6-Chloro-2-pyrazinyl)-2-methylpiperazine, Maleate.
A mixture of 2.6-dichloropyrazine (2.33 g, 15.7 mmol), the product from step 1 above (5.11 g, 14.9 mmol) and K_2CO_3 (3.09 g, 22.4 mmol) in dry DMF (50 mL) was stirred at 120 °C for 7.5 h. The dark reaction mixture was diluted with ether and solids were filtered off. The filter cake was washed with $CHCl_3$. The filtrate was concentrated under reduced pressure. The residue was redissolved in $CHCl_3$ (150 mL) and 5M aqueous HCl (20 mL) was added and the mixture was stirred at room temperature 8.5 h. A solution of 5 M aqueous NaOH (25 mL) was added carefully and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 x 150 mL). The combined, dried (K_2CO_3), organic phases were concentrated *in vacuo*. The brownish oily residue was purified by silica gel chromatography (bed size: 11 x 6 cm) using $CHCl_3$/MeOH (92:8) as eluent. The yield of the free base of the title compound was 1.74 g (55%) which was obtained as a tan colored oil. A portion (0.41 g, 1.9 mmol) of the free base was converted into its maleate salt. Purity 99% (HPLC). HRMS *m/z* calcd for $C_9H_{13}ClN_4$ $(M)^+$ 212.0829, found 212.0819.

Step 3: (2*R*)-1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine, Maleate.
K-*t*-BuO (2.07 g, 18.4 mmol) was added to a mixture of (2*R*)-1-(6-chloro-2-pyrazinyl)-2-methylpiperazine (prepared in step 2 above; 1.31 g, 6.15 mmol) and benzyl alcohol (10.0 g, 92.5 mmol). After being stirred for 7 h at 95 °C, the mixture was applied onto a bed of silica (12 x 6 cm). Elution with $CHCl_3$/MeOH (97:3 followed by 92:8) furnished 1.44 g (82%) of the free base of the title compound as a light yellow oil. The free base was converted into its maleate salt. Purity 99% (HPLC). MS *m/z* 284 $(M)^+$. HRMS *m/z* calcd for $C_{16}H_{20}N_4O$ $(M)^+$ 284.1637, found 284.1633.

EXAMPLE 63

(2*R*)-1-[6-(Benzyloxy)-4-(trifluoromethyl)-2-pyridinyl]-2-methylpiperazine.
The title compound was prepared according to the procedure of example 40 with the exceptions that (2*R*)-methylpiperazine was substituted for (2*S*)-methylpiperazine in step 1 and that *N*-deprotection (*N*-detritylation) in step 2 was carried out using trifluoroacetic acid in dichloromethane (3:1). MS *m/z* 352 $(M + H)^+$. HRMS *m/z* calcd for $C_{18}H_{20}F_3N_3O$ $(M)^+$ 351.1558, found 351.1549.

EXAMPLE 64

(2*R*)-1-[6-(Benzyloxy)-2-pyridinyl]-2-methylpiperazine.
The title compound was prepared according to the procedure of example 39 with the exceptions that (2*R*)-methylpiperazine was substituted for (2*S*)-methylpiperazine in step 1, and that 2,6-dichloropyridine was substituted for 2,6-dichloropyrazine in step 2, and further that *N*-deprotection (*N*-detritylation) in step 2 was carried out using trifluoroacetic acid in dichloromethane (3:1). MS *m/z* 284 $(M + H)^+$.

EXAMPLE 65

2-(1-Piperazinyl)-6-{[3-(1*H*-pyrrol-1-yl)-2-thienyl]methoxy}pyrazine.

Step 1: 2-Chloro-6-{[3-(1*H*-pyrrol-1-yl)-2-thienyl]methoxy}pyrazine.
The title compound was prepared according to the procedure of example 50, step 1, starting from 3-(pyrrol-1-yl)thiophene-2-methanol (2.5 g, 14 mmol), K-*t*-BuO (1.43 g, 12.7 mmol) and 2,6-dichloropyrazine (1.73 g, 11.6 mmol). The yield of the title compound was 3.05 g (90%) and was obtained as an oil. Anal. ($C_{13}H_{10}ClN_3OS$) C, H, N.

Step 2: 2-(1-Piperazinyl)-6-{[3-(1*H*-pyrrol-1-yl)-2-thienyl]methoxy}pyrazine.
The title compound was prepared according to the procedure of example 50, step 2, starting from the product obtained in step 1 above (1.78 g, 6.10 mmol), piperazine (1.58 g, 18.3 mmol) and K_2CO_3 (0.86 g, 6.2 mmol). The yield of the title compound was 1.43 g (69%) and was obtained as a beige solid. HRMS *m/z* calcd for $C_{17}H_{19}N_5OS$ $(M)^+$ 341.1310, found 341.1301.

EXAMPLE 66

2-{[3-(Benzyloxy)benzyl]oxy}-6-(1-piperazinyl)pyrazine.

Step 1: 2-{[3-(Benzyloxy)benzyl]oxy}-6-chloropyrazine.

The title compound was prepared according to the procedure of example 50, step 1, starting from 3-benzyloxybenzyl alcohol (3.46 g, 16.2 mmol), K-*t*-BuO (1.69 g, 15.1 mmol) and 2,6-dichloropyrazine (1.97 g, 13.2 mmol). The yield of the title compound was 2.64 g (61%) and was obtained as a semisolid. Anal. ($C_{18}H_{15}ClN_2O_2$) C, H, N.

Step 2: 2-{[3-(Benzyloxy)benzyl]oxy}-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from the product obtained in step 1 above (1.62 g, 4.96 mmol), piperazine (1.28 g, 14.9 mmol) and K_2CO_3 (0.70 g, 5.1 mmol). The yield of the title compound was 1.16 g (62%) and was obtained as an oil. HRMS *m/z* calcd for $C_{22}H_{24}N_4O_2$ (M)$^+$ 376.1899, found 376.1890. Anal. ($C_{22}H_{24}N_4O_2$) C, H, N.

EXAMPLE 67

2-(1-Piperazinyl)-6-[3-(2-pyridinyl)propoxy]pyrazine, Maleate.

Step 1: 2-Chloro-6-[3-(2-pyridinyl)propoxy]pyrazine.

The title compound was prepared according to the procedure of example 50, step 1, starting from 2-pyridinepropanol (4.08 g, 29.7 mmol), K-*t*-BuO (3.17 g, 28.3 mmol) and 2,6-dichloropyrazine (3.69 g, 24.8 mmol). The yield of the title compound was 5.18 g (84%) and was obtained as an oil. Anal. ($C_{12}H_{12}ClN_3O$) C, H, N.

Step 2: 2-(1-Piperazinyl)-6-[3-(2-pyridinyl)propoxy]pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from the product obtained in step 1 above (1.80 g, 7.20 mmol), piperazine (1.87 g, 21.6 mmol) and K_2CO_3 (1.0 g, 7.2 mmol). The free base (1.23 g) of the title compound was converted into its maleate. Recrystallization from MeOH-ether furnished 1.32 g (38%) of the title compound. HRMS *m/z* calcd for $C_{16}H_{21}N_5O$ (M)$^+$ 299.1758, found 299.1748. Anal. ($C_{16}H_{21}N_5O \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

EXAMPLE 68

2-[(3,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Maleate.

Step 1: 2-Chloro-6-[(3,5-dimethoxybenzyl)oxy]pyrazine.

The title compound was prepared according to the procedure of example 50, step 1, starting from 3,5-dimethoxybenzyl alcohol (2.16 g, 12.8 mmol), K-*t*-BuO (1.34 g, 11.9 mmol) and 2,6-dichloropyrazine (1.59 g, 10.7 mmol). The yield of the title compound was 2.56 g (84%) and was obtained as a white solid. HRMS *m/z* calcd for $C_{13}H_{13}ClN_2O_3$ $(M)^+$ 280.0615, found 280.0627. Anal. ($C_{13}H_{13}ClN_2O_3$) C, H, N.

Step 2: 2-[(3,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from the product obtained in step 1 above (1.26 g, 4.50 mmol), piperazine (1.12 g, 13.0 mmol) and K_2CO_3 (0.62 g, 4.5 mmol). The free base (1.14 g) of the title compound was converted into its maleate salt. Recrystallization from MeOH-ether furnished 1.05 g (68%) of the title compound: mp 134-137 °C. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_3$ $(M)^+$ 330.1692, found 330.1699. Anal. ($C_{17}H_{22}N_4O_3 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 69

2-[2-(4-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

Step 1: 2-Chloro-6-[2-(4-methoxyphenyl)ethoxy]pyrazine.

The title compound was prepared according to the procedure of example 50, step 1, starting from 4-methoxyphenethyl alcohol (1.99 g, 13.1 mmol), K-*t*-BuO (1.34 g, 12.0 mmol) and 2,6-dichloropyrazine (1.56 g, 10.5 mmol). The yield of the title compound was 2.14 g (77%) and was obtained as a white solid. Anal. ($C_{13}H_{13}ClN_2O_2$) C, H, N.

Step 2: 2-[2-(4-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from the product obtained in step 1 above (1.31 g, 4.95 mmol), piperazine (1.24 g, 14.4 mmol) and K_2CO_3 (0.68 g, 4.9 mmol). The free base (1.29 g) of the title compound was converted into its maleate salt. Recrystallization from MeOH-ether

furnished 1.41 g (79%) of the title compound: mp 149-151 °C. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_2$ $(M)^+$ 314.1743, found 314.1727. Anal. ($C_{17}H_{22}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 70

2-[2-(4-Methyl-1,3-thiazol-5-yl)ethoxy]-6-(1-piperazinyl)pyrazine, Acetate.

The title compound was prepared according to the procedure of example 42 starting from 4-methyl-5-hydroxyethyl thiazole (0.215 g, 1.50 mmol) and was isolated as a brown oil. Yield: 0.41 g (66%). HRMS *m/z* calcd for $C_{14}H_{19}N_5OS$ $(M)^+$ 305.1310, found 300.1325. Anal. ($C_{14}H_{19}N_5OS \cdot 1.5CH_3COOH \cdot 0.7H_2O$).

General procedure for synthesis of the title compounds described in Examples 71-96.

To the appropriate alcohol or thiol (1.8 mmol) in dry DMF (5 mL) was added Na-*t*-BuO (1.20 ml, 2.5 M in DMF) and the mixture was stirred at room temperature for 15 minutes. To the mixture was added a solution of the appropriate piperazino-substituted chloro heterocycle (0.625 mL, 2.0 M in DMF) and the mixture were stirred at 100 °C for 5 h. The reactions were quenched with water (0.2 mL) and the solvent was removed under reduced pressure. The residue was taken up in water/$CHCl_3$ (20:80; 5 mL) and applied onto a column of Hydromatrix (40 mL) to which water (5 mL) had been added. Elution with $CHCl_3$ (4 x 8 mL) furnished the crude products. Concentration under reduced pressure and purification of the residues by preparative HPLC furnished the desired products as their acetic acid salts.

EXAMPLE 71

2-[2-(3-Methoxyphenoxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt.

Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine*, and 2-(3-methoxyphenoxy)-ethanol. Purity 90% (HPLC). Fragmenting mass analysis supports the stated structure. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_3$ $(M)^+$ 330.1692, found 330.1681.

*Obtained in Example 13, step 2.

EXAMPLE 72

2-[2-(2,6-Difluorophenoxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(2,6-difluorophenoxy)-ethanol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{16}H_{18}F_2N_4O_3$ $(M)^+$ 336.1398, found 336.1403.

EXAMPLE 73

2-[2-(Quinolin-8-yloxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(quinolin-8-yloxy)ethanol.*

Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{19}H_{21}N_5O_2$ $(M)^+$ 351.1695, found 351.1683. *Described in WO 00/76984.

EXAMPLE 74

2-[(2*R*)-2,3-Dihydro-1,4-benzodioxin-2-ylmethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt.

Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (2*R*)-2-hydroxymethyl-1,4-benzodioxan*. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{17}H_{20}N_4O_3$ $(M)^+$ 328.1535, found 328.1524. *Described in Tetrahedron Lett. 1988, 29, 3671-4.

EXAMPLE 75

2-[2-(2-Naphthyloxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(naphthalen-2-yloxy)-ethanol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{20}H_{22}N_4O_2$ $(M)^+$ 350.1743, found 350.1752

EXAMPLE 76

2-{2-[(2-Ethoxy-3-pyridinyl)oxy]ethoxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(2-ethoxypyridin-3-yloxy)-ethanol*. Fragmenting mass analysis supports the stated structure. Purity

80% (HPLC). HRMS *m/z* calcd for $C_{17}H_{23}N_5O_3$ $(M)^+$ 345.1801, found 345.1793. *Described in WO 00/76984.

EXAMPLE 77

2-{[4-(Benzyloxy)-3-methoxybenzyl]oxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (4-benzyloxy-3-methoxyphenyl)-methanol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{23}H_{26}N_4O_3$ $(M)^+$ 406.2005, found 406.1967.

EXAMPLE 78

2-{[5-(Phenylethynyl)-2-thienyl]methoxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (5-phenylethynyl-thiophen-2-yl)-methanol. Fragmenting mass analysis supports the stated structure Purity 80% (HPLC). HRMS *m/z* calcd for $C_{21}H_{20}N_4OS$ $(M)^+$ 376.1358, found 376.1346.

EXAMPLE 79

2-(2,3-Dihydro-1,4-benzodioxin-6-ylmethoxy)-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (2,3-dihydro-1,4-benzodioxin-6-yl)-methanol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{17}H_{20}N_4O_3$ $(M)^+$ 328.1535, found 328.1543.

EXAMPLE 80

2-(1-Methyl-2-phenylethoxy)-6-(1-piperazinyl)pyrazine, Acetic acid salt. The general procedure was followed with the exception that the reaction mixture was heated at 100 °C overnight. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 1-phenylpropan-2-ol. Fragmenting mass analysis supports the stated structure. Purity 70% (HPLC). HRMS *m/z* calcd for $C_{17}H_{22}N_4O$ $(M)^+$ 298.1794, found 298.1801.

EXAMPLE 81

2-[(2-Chlorobenzyl)sulfanyl]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (2-chlorophenyl)-methanethiol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{15}H_{17}ClN_4S$ $(M)^+$ 320.0862, found 320.0868

EXAMPLE 82

2-[(2-Phenylethyl)sulfanyl]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-phenyl-ethanethiol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{16}H_{20}N_4S$ $(M)^+$ 300.1409, found 300.1419.

EXAMPLE 83

2-[(4-Phenoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials 2-chloro-6-(1-piperazinyl)pyrazine and 4-phenoxybenzyl alcohol*. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{21}H_{22}N_4O_2$ $(M)^+$ 362.1743, found 362.1738. *Prepared by reduction of 4-phenoxybenzaldehyde.

EXAMPLE 84

2-{[4-(3-Dimethylamino-propoxy)benzyl]oxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and [4-(3-dimethylamino-propoxy)-phenyl]-methanol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{20}H_{29}N_5O_2$ $(M)^+$ 371.2321, found 371.2314.

EXAMPLE 85

2-{2-[2-(Benzyloxy)phenyl]ethoxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(2-benzyloxy-phenyl)-ethanol.* Fragmenting mass analysis supports the stated structure. Purity 70%

(HPLC). HRMS *m/z* calcd for $C_{23}H_{26}N_4O_2$ $(M)^+$ 390.2056, found 390.2043. *Prepared by reduction of (2-benzyloxy-phenyl)-acetic acid.

EXAMPLE 86

2-[2-(2,5-Dimethoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(2,5-dimethoxy-phenyl)-ethanol*. Fragmenting mass analysis supports the stated structure. Purity 80% (HPLC). HRMS *m/z* calcd for $C_{18}H_{24}N_4O_3$ $(M)^+$ 344.1848, found 344.1861. *Prepared by reduction of (2,5-dimethoxy-phenyl)-acetic acid.

EXAMPLE 87

2-(1-Benzofuran-2-ylmethoxy)-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and benzofuran-2-yl-methanol.* Fragmenting mass analysis supports the stated structure. Purity 80% (HPLC). HRMS *m/z* calcd for $C_{17}H_{18}N_4O_2$ $(M)^+$ 310.1430, found 310.1419. *Prepared by reduction of benzofuran-2-carbaldehyde.

EXAMPLE 88

2-{2-[3-Methoxy-2-(phenoxymethyl)phenyl]ethoxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (3-methoxy-2-phenoxymethyl-phenyl)-methanol.* Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{23}H_{26}N_4O_3$ $(M)^+$ 406.2005, found 406.2011. *Prepared by reduction of 3-methoxy-2-phenoxymethyl-benzaldehyde.

EXAMPLE 89

2-[2-(Isoquinolin-7-yloxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt.

Step 1: 2-(7-Isoquinolinyloxy)ethanol.

A mixture of 7-hydroxyisoquinoline (1.15 g, 7.9 mmol), ethylene carbonate (0.98 g, 11.1 mmol), powdered K_2CO_3 (0.65 g, 4.7 mmol) in dry DMF (20 mL) was stirred at 145 °C for two hours. The reaction was quenched with MeOH (1 mL), filtered and

the solvent was removed under reduced pressure. The residue was taken up between alkaline water (K_2CO_3) and $CHCl_3$. Concentration of the dried ($MgSO_4$) organic phase afforded 1.4 g (94%) of the title compound as a yellow oil that solidified upon standing. Purity 91% (HPLC). Fragmenting mass analysis supports the stated structure.

Step 2: 2-[2-(Isoquinolin-7-yloxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt. The general procedure was followed starting 2-chloro-6-(1-piperazinyl)pyrazine and 2-(7-isoquinolinyloxy)ethanol. Fragmenting mass analysis supports the stated structure. Purity 80% (HPLC). HRMS *m/z* calcd for $C_{19}H_{21}N_5O_2$ $(M)^+$ 351.1695, found 351.1696.

EXAMPLE 90

2-(2,3-Dihydro-1*H*-inden-2-yloxy)-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-indanol. The general procedure was followed with the exception that the reaction mixture was heated at 100 °C overnight. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{17}H_{20}N_4O$ $(M)^+$ 296.1637, found 296.1652.

EXAMPLE 91

2-{[2-(Phenoxymethyl)benzyl]oxy}-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-phenoxymethyl-benzyl alcohol.* Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{22}H_{24}N_4O_2$ $(M)^+$ 376.1899, found 376.1889.

*Prepared by reduction of 2-phenoxymethylbenzoic acid by lithium aluminum hydride in THF, *cf* J. Chem. Soc. 1954, 2819.

EXAMPLE 92

2-(2-Cyclohexylethoxy)-6-(1-piperazinyl)pyrazine, Acetic acid salt. Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-cyclohexyl-ethanol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{16}H_{26}N_4O$ $(M)^+$ 290.2107, found 290.2109.

EXAMPLE 93

2-[2-(2-Amino-quinolin-8-yloxy)ethoxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt.

Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 2-(2-amino-quinolin-8-yloxy)-ethanol.* Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{19}H_{22}N_6O_2$ $(M)^+$ 366.1804, found 366.1791. *Prepared as described in WO 00/76984.

EXAMPLE 94

2-[(3-Cyanobenzyl)oxy]-6-(1-piperazinyl)pyrazine.

Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 3-cyanobenzyl alcohol. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{16}H_{17}N_5O$ $(M)^+$ 295.1433, found 295.1431.

EXAMPLE 95

2-[(5-Fluoro-2-methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Acetic acid salt.

Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and (5-fluoro-2-methoxy-phenyl)-methanol.* Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{16}H_{19}FN_4O_2$ $(M)^+$ 318.1492, found 318.1490. *Prepared by reduction of 5-fluoro-2-methoxybenzaldehyde.

EXAMPLE 96

2-(1-Cyclopentylethoxy)-6-(1-piperazinyl)pyrazine, Acetic acid salt.

Starting materials, 2-chloro-6-(1-piperazinyl)pyrazine and 1-cyclopentyl-ethanol. The general procedure was followed with the exceptions that dioxane was used as solvent and that the reaction mixture was heated in a sealed tube with microwaves at 160 °C for 20 minutes. Fragmenting mass analysis supports the stated structure. Purity 90% (HPLC). HRMS *m/z* calcd for $C_{15}H_{24}N_4O$ $(M)^+$ 276.1950, found 276.1955.

EXAMPLE 97

2-[(2,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(2,5-difluorobenzyl)oxy]pyrazine (3.43 g, 13.4 mmol; obtained according to the procedure of example 50, step 1, starting from 2,5-difluorobenzyl alcohol), piperazine (3.51 g, 40.7 mmol) and K_2CO_3 (1.94 g, 14.0 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 2.84 g (69%) which was obtained as an oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 306 $(M)^+$. HRMS *m/z* calcd for $C_{15}H_{16}F_2N_4O$ $(M)^+$ 306.1292, found 306.1297.

EXAMPLE 98

2-[(3-Dimethylaminobenzyl)oxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(3-dimethylaminobenzyl)oxy]pyrazine (3.04 g, 11.5 mmol; obtained according to the procedure of example 50, step 1, starting from 3-dimethylaminobenzyl alcohol), piperazine (3.08 g, 35.7 mmol) and K_2CO_3 (1.59 g, 11.5 mmol) with the exception that the final filtration through alumina was omitted. The yield of the of the title compound was 2.06 g (57%) which was obtained as a beige colored oil that solidified when refrigerated. Purity 98% (HPLC). MS *m/z* 313 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{23}N_5O$ $(M)^+$ 313.1903, found 313.1910.

EXAMPLE 99

2-[{4-(2-Pyridinyl)benzyl}oxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[{4-(2-pyridinyl)benzyl}oxy]pyrazine (2.73 g, 9.16 mmol; obtained according to the procedure of example 50, step 1, starting from 4-(2-pyridinyl)benzyl alcohol*), piperazine (2.41 g, 27.9 mmol) and K_2CO_3 (1.33 g, 9.62 mmol) with the exception that the final filtration through alumina was omitted. The yield of the of the title compound was 2.06 g (65%) which was obtained as a beige colored oil that solidified when refrigerated. Purity 100% (HPLC). MS *m/z* 347 $(M)^+$. HRMS *m/z* calcd for $C_{20}H_{21}N_5O$ $(M)^+$ 347.1746, found 347.1749. *Obtained by reduction ($NaBH_4$) of 4-(2-pyridyl)benzaldehyde.

EXAMPLE 100

2-[(2-Fluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(2-fluorobenzyl)oxy]pyrazine (3.68 g, 15.4 mmol; obtained according to the procedure of example 50, step 1, starting from 2-fluorobenzyl alcohol), piperazine (4.06 g, 47.1 mmol) and K_2CO_3 (2.24 g, 16.2 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 3.28 g (74%) which was obtained as an oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 288 $(M)^+$. HRMS *m/z* calcd for $C_{15}H_{17}FN_4O$ $(M)^+$ 288.1386, found 288.1378.

EXAMPLE 101

2-(Benzo[*b*]thiophen-3-ylmethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(benzo[*b*]thiophen-3-ylmethoxy)pyrazine (2.88 g, 10.4 mmol; obtained according to the procedure of example 50, step 1, starting from benzo[*b*]thiophene-3-methanol), piperazine (2.73 g, 31.7 mmol) and K_2CO_3 (1.51 g, 10.9 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 2.34 g (69%) which was obtained as a beige colored oil. The free base was converted into its maleate salt. Purity 99% (HPLC). MS *m/z* 326 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{18}N_4OS$ $(M)^+$ 326.1201, found 326.1207.

EXAMPLE 102

2-(3-Phenoxy-thiophen-2-ylmethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(3-phenoxy-thiophen-2-ylmethoxy)pyrazine [2.83 g, 8.88 mmol; obtained according to the procedure of example 50, step 1, starting from (3-phenoxy-2-thienyl)methanol], piperazine (2.33 g, 27.1 mmol) and K_2CO_3 (1.29 g, 9.3 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 1.80 g (55%) which was obtained as a beige colored oil. The free base was converted into its maleate salt.

Purity 98% (HPLC). MS *m/z* 368 $(M)^+$. HRMS *m/z* calcd for $C_{19}H_{20}N_4O_2S$ $(M)^+$ 368.1307, found 368.1306.

EXAMPLE 103

2-[5-(2-Pyridinyl)-thiophen-2-ylmethoxy)]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[5-(2-pyridinyl)-thiophen-2-ylmethoxy)]pyrazine [2.17 g, 7.13 mmol; obtained according to the procedure of example 50, step 1, starting from 5-(pyridin-2-yl)thiophene-2-methanol], piperazine (1.84 g, 21.4 mmol) and K_2CO_3 (0.99 g, 7.1 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 1.66 g (66%) which was obtained as a beige colored oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 353 $(M)^+$. HRMS *m/z* calcd for $C_{18}H_{19}N_5OS$ $(M)^+$ 353.1310, found 353.1307.

EXAMPLE 104

2-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]pyrazine [2.90 g, 9.18 mmol; obtained according to the procedure of example 50, step 1, starting from 2-(5-methyl-2-phenyloxazol-4-yl)ethanol], piperazine (2.37 g, 27.5 mmol) and K_2CO_3 (1.27 g, 9.19 mmol) with the exception that the final filtration through alumina was omitted. The yield of the of the title compound was 2.09 g (62%) which was obtained as a light yellow oil that solidified when refrigerated. Purity 100% (HPLC). MS *m/z* 365 $(M)^+$. HRMS *m/z* calcd for $C_{20}H_{23}N_5O_2$ $(M)^+$ 365.1852, found 365.1855.

EXAMPLE 105

2-[1-(2,6-Difluoro-phenyl)-ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[1-(2,6-difluoro-phenyl)-ethoxy]pyrazine (3.20 g, 11.8 mmol; obtained according to the procedure of example 50, step 1, starting from 2,6-

difluoro-α-methylbenzyl alcohol), piperazine (3.05 g, 35.4 mmol) and K_2CO_3 (1.63 g, 11.8 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 2.95 g (78%) which was obtained as a colorless oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 320 $(M)^+$. HRMS *m/z* calcd for $C_{16}H_{18}F_2N_4O$ $(M)^+$ 320.1449, found 320.1447.

EXAMPLE 106

2-(2-Naphthalen-2-yl-ethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(2-naphthalen-2-yl-ethoxy)pyrazine (2.73 g, 9.60 mmol; obtained according to the procedure of example 50, step 1, starting from 2-naphthalene-ethanol), piperazine (2.89 g, 33.5 mmol) and K_2CO_3 (1.39 g, 10.1 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 2.63 g (82%) which was obtained as a colorless oil. The free base was converted into its maleate salt. Purity 99% (HPLC). MS *m/z* 334 $(M)^+$. HRMS *m/z* calcd for $C_{20}H_{22}N_4O$ $(M)^+$ 334.1794, found 334.1794.

EXAMPLE 107

2-[3-(Naphthalen-2-yloxy)-propoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[3-(naphthalen-2-yloxy)-propoxy]pyrazine [2.24 g, 7.12 mmol; obtained according to the procedure of example 50, step 1, starting from 3-(naphthalen-2-yloxy)-propan-1-ol*], piperazine (1.90 g, 22.1 mmol) and K_2CO_3 (1.03 g, 7.45 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 1.10 g (42%) which was obtained as a light beige colored oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 364 $(M)^+$. HRMS *m/z* calcd for $C_{21}H_{24}N_4O_2$ $(M)^+$ 364.1899, found 364.1895. *Described in J. Am. Chem Soc. 1929, 51, 3417 and *ibid.* 1954, 76, 56.

EXAMPLE 108

2-(4-Phenylethynyl-thiophen-2-ylmethoxy)-6-(1-piperazinyl)pyrazine, Maleate. The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(4-phenylethynyl-thiophen-2-ylmethoxy)pyrazine [2.05 g, 6.28 mmol; obtained according to the procedure of example 50, step 1, starting from 4-(phenylethynyl)thiophene-2-methanol*], piperazine (1.62 g, 18.8 mmol) and K_2CO_3 (0.89 g, 6.4 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 1.80 g (76%) which was obtained as a light beige colored oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 376 $(M)^+$. HRMS *m/z* calcd for $C_{21}H_{20}N_4OS$ $(M)^+$ 376.1358, found 376.1351. *Obtained by reduction ($NaBH_4$) of 4-(phenylethynyl)thiophene-2-carboxaldehyde.

EXAMPLE 109

2-(1-Cyclopropyl-ethoxy)-6-(1-piperazinyl)pyrazine, Maleate. The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(1-cyclopropyl-ethoxy)pyrazine (2.38 g, 12.0 mmol; obtained according to the procedure of example 50, step 1, starting from α-methylcyclopropanemethanol), piperazine (3.60 g, 41.8 mmol) and K_2CO_3 (1.75 g, 12.7 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 2.05 g (69%) which was obtained as a colorless oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 248 $(M)^+$. HRMS *m/z* calcd for $C_{13}H_{20}N_4O$ $(M)^+$ 248.1637, found 248.1636.

EXAMPLE 110

2-[2-(6-Methoxy-naphthalen-2-yloxy)-ethoxy]-6-(1-piperazinyl)pyrazine. The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(6-methoxy-naphthalen-2-yloxy)-ethoxy]pyrazine [0.94 g, 2.8 mmol; obtained according to the procedure of example 50, step 1, starting from 2-(6-methoxy-naphthalen-2-yloxy)ethanol*], piperazine (1.00 g, 11.6 mmol) and K_2CO_3 (0.50 g, 3.6 mmol) with the exception that the final filtration through alumina was omitted. The yield of the of the title compound was 0.52 g (48%) which

was obtained as a beige colored solid. Purity 100% (HPLC). MS *m/z* 380 $(M)^+$. HRMS *m/z* calcd for $C_{21}H_{24}N_4O_3$ $(M)^+$ 380.1848, found 380.1845. *Prepared from 6-methoxy-2-naphthol and ethylene carbonat according to the procedure of Example 134, step 1, in WO 00/76984. The reaction mixture was refluxed for 2 h. Pure 2-(6-methoxy-naphthalen-2-yloxy)ethanol was obtained by recrystallization from MeOH/$CHCl_3$/*n*-hexane.

EXAMPLE 111

2-[2-(7-Methoxy-naphthalen-2-yloxy)-ethoxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(7-methoxy-naphthalen-2-yloxy)-ethoxy]pyrazine [1.19 g, 3.60 mmol; obtained according to the procedure of example 50, step 1, starting from 2-(7-methoxy-naphthalen-2-yloxy)ethanol*], piperazine (1.25 g, 14.5 mmol) and K_2CO_3 (0.60 g, 4.3 mmol) with the exception that the final filtration through alumina was omitted. The yield of the of the title compound was 0.98 g (71%) which was obtained as an oil that solidified when refrigerated. Purity 100% (HPLC). MS *m/z* 380 $(M)^+$. HRMS *m/z* calcd for $C_{21}H_{24}N_4O_3$ $(M)^+$ 380.1848, found 380.1851. *Prepared from 7-methoxy-2-naphthol and ethylene carbonat according to the procedure of Example 134, step 1, in WO 00/76984. The reaction mixture was refluxed for 2 h. Pure 2-(7-methoxy-naphthalen-2-yloxy)ethanol was obtained after column chromatography on silica gel using *n*-hexane/ethyl acetate (6:4) as eluent.

EXAMPLE 112

2-[5-(4-Chlorophenyl)-2-methylfuran-3-ylmethoxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[5-(4-chlorophenyl)-2-methylfuran-3-ylmethoxy]pyrazine [3.14 g, 9.39 mmol; obtained according to the procedure of example 50, step 1, starting from 5-(4-chlorophenyl)-3-hydroxymethyl-2-methylfuran], piperazine (2.47 g, 28.6 mmol) and K_2CO_3 (1.36 g, 9.86 mmol) with the exception that the final filtration through alumina was omitted. The yield of the of the title compound was 2.11 g (58%) which was obtained as a beige colored solid. Purity 100% (HPLC). MS *m/z* 384 $(M)^+$. HRMS *m/z* calcd for $C_{20}H_{21}ClN_4O_2$ $(M)^+$ 384.1353, found 384.1357.

EXAMPLE 113

2-(1*H*-Indol-4-ylmethoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(1*H*-indol-4-ylmethoxy)pyrazine [0.486 g, 1.87 mmol; obtained according to the procedure of example 50, step 1, starting from (1*H*-indol-4-yl)-methanol*], piperazine (0.491 g, 5.71 mmol) and K_2CO_3 (0.272 g, 1.96 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 0.198 g (34%) which was obtained as an oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 309 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{19}N_5O$ $(M)^+$ 309.1590, found 309.1582. *The reaction was carried out using (1*H*-indol-4-yl)-methanol (0.712 g, 4.84 mmol), K-*t*-BuO (0.517 g, 4.61 mmol), and 2,6-dichloropyrazine (0.687 g, 4.61 mmol).

EXAMPLE 114

2-(2-Phenyl-propoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(2-phenyl-propoxy)pyrazine (2.39 g, 9.61 mmol; obtained according to the procedure of example 50, step 1, starting from 2-phenyl-1-propanol), piperazine (2.90 g, 3.36 mmol) and K_2CO_3 (1.40 g, 10.1 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 1.66 g (58%) which was obtained as a colorless oil.

The free base was converted into its maleate salt. Purity 99% (HPLC). HRMS *m/z* calcd for $C_{17}H_{22}N_4O$ $(M)^+$ 298.1794, found 298.1795.

EXAMPLE 115

2-[2-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(2-methoxyphenyl)ethoxy]pyrazine (0.967 g, 3.65 mmol; obtained according to the procedure of example 50, step 1, starting from 2-methoxyphenethyl alcohol), piperazine (0.913 g, 10.6 mmol) and K_2CO_3 (0.505 g, 3.65 mmol). The yield of the free base of the title compound was 0.63 g (55%) which was obtained as a colorless oil. The free base was converted into its maleate salt. Purity 100% (HPLC). MS *m/z* 314 $(M)^+$. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_2$ $(M)^+$ 314.1743, found 314.1750.

EXAMPLE 116

2-[2-(3-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[2-(3-methoxyphenyl)ethoxy]pyrazine (1.12 g, 4.23 mmol; obtained according to the procedure of example 50, step 1, starting from 3-methoxyphenethyl alcohol), piperazine (1.06 g, 12.3 mmol) and K_2CO_3 (0.585 g, 4.23 mmol). The yield of the title compound was 0.91 g (69%) which was obtained as light beige oil. HRMS *m/z* calcd for $C_{17}H_{22}N_4O_2$ $(M)^+$ 314.1743, found 314.1759. Anal. ($C_{17}H_{22}N_4O_2$) C, H, N.

EXAMPLE 117

2-[(2-Phenoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-[(2-phenoxybenzyl)oxy]pyrazine (0.981 g, 3.14 mmol; obtained according to the procedure of example 50, step 1, starting from 2-phenoxybenzyl alcohol), piperazine (0.784 g, 9.10 mmol) and K_2CO_3 (0.434 g, 3.14 mmol) with the exception that the final filtration through alumina was omitted. The yield of the free base of the title compound was 0.80 g (70%) which was obtained as

a colorless oil. The free base was converted into its maleate salt. Anal. ($C_{21}H_{22}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 118

2-Benzylamino-4-(1-piperazinyl)pyrimidine, Hydrochloride.

Step 1: 2-Benzylamino-4-[1-(4-*tert*-butoxycarbonyl)piperazinyl]pyrimidine.

A mixture of 2-chloro-4-[1-(4-*tert*-butoxycarbonyl)piperazinyl]pyrimidine (obtained in Example 33, step 1; 1.80 g, 6.02 mmol), benzylamine (10 mL, large excess) and potassium carbonate (0.91 g, 6.62 mmol) was stirred in 50 mL of propionitrile at 110 °C for 1.5 h. The mixture was poured into water (200 mL) and left over night. The title compound was collected, washed with water + 10% methanol and dried. Yield: 2.08 g (94%). Purity >90% (HPLC). HRMS *m/z* calcd for $C_{20}H_{27}N_5O_2$ $(M)^+$ 369.2165, found 369.2152.

Step 2: 2-Benzylamino-4-(1-piperazinyl)pyrimidine, Hydrochloride.

To a solution of 2-benzylamino-4-[1-(4-*tert*-butoxycarbonyl)piperazinyl]pyrimidine (37 mg, 0.10 mmol) in a mixture of methyl tert butyl ether (3 mL) and methanol (1 mL) was 4.0 M HCl in dioxane (1 mL) added. The reaction was shaken over night. Methyl tert butyl ether (2 mL) was added. The title compound was collected as a white solid. Yield: 29 mg (95%). Purity >90% (HPLC). MS *m/z* 270 $(M+H)^+$.

EXAMPLE 119

(2*R*)-1-[6-{(2-Chlorobenzyl)sulfanyl}-2-pyrazinyl]-2-methylpiperazine, Hydrochloride.

Na-*t*-BuO (8.7 mmol 0.84 g) was added to a solution of 2-chlorobenzylthiol (5.7 mmol 0.90 g) in dry DMF (25 mL) and the mixture was stirred at room temperature for 10 minutes. (2*R*)-1-(6-chloro-2-pyrazinyl)-2-methylpiperazine (0.92 g, 4.35 mmol; obtained in Example 62, step 2) was added and the reaction was stirred at 70 °C for 2 h. The mixture was filtered through a plug of silica and the solvent from the filtrate was evaporated at reduced pressure. The brown residue was chromatographed over silica gel using $CHCl_3$/MeOH/aq NH_3 90/10/0.25 as eluent. This furnished the free base of the title compound as a yellow oil. The free base was precipitated as its

HCl salt with HCl/ether to give 1.10 g (68%) of the title compound as light yellow crystals. Purity 98% (HPLC). HRMS *m/z* for $C_{16}H_{19}ClN_4S$ $(M)^+$ calcd for 334.1019, found 334.1036.

EXAMPLE 120

2-(3-Thienylmethoxy)-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of Example 20 starting from 3-thiophenemethanol (6.05 g, 53.0 mmol), K-*t*-BuO (0.897 g, 7.99 mmol) and 6-chloro-2-(1-piperazinyl)pyrazine (0.845 g, 4.25 mmol: obtained in Example 13, step 2). The reaction mixture was stirred at 105 °C for 7.5 h. Following chromatography on silica, solvents were evaporated off. The remaining oil was redissolved in ethyl acetetate and filtered through a short plug of alumina (5 x 3 cm) using ether/MeOH (96:4) as eluent. Solvent removal *in vacuo* gave 0.76 g (64%) of the title compound as a colorless oil. HRMS *m/z* for $C_{13}H_{16}N_4OS$ $(M)^+$ calcd for 276.1045, found 276.1037. Anal. ($C_{13}H_{16}N_4OS \cdot 0.25\ H_2O$) C, H, N.

EXAMPLE 121

2-(3-Phenoxypropoxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(3-phenoxypropoxy)pyrazine (1.04 g, 3.93 mmol; obtained according to the procedure of example 50, step 1, starting from 3-phenoxy-1-propanol), piperazine (0.981 g, 11.4 mmol) and K_2CO_3 (0.543 g, 3.93 mmol). Following chromatography on silica, solvents were evaporated off. The semi-solid residue (0.83 g) was redissolved in $CHCl_3$ and filtered. The clear solution was concentrated *in vacuo* and the resulting free base of the title compound was converted into its maleate salt. Yield: 0.90 g (53%). HRMS *m/z* calcd for $C_{17}H_{22}N_4O_2$ $(M)^+$ 314.1743, found 314.1728. Anal. ($C_{17}H_{22}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 122

2-{[4-(Benzyloxy)benzyl]oxy}-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-{[4-(benzyloxy)benzyl]oxy}pyrazine (1.15 g, 3.52 mmol; obtained according to the procedure of example 50, step 1, starting from 4-benzyloxybenzyl alcohol), piperazine (0.894 g, 10.4 mmol) and K_2CO_3 (0.486 g, 3.52 mmol). The yield of the title compound was 0.57 g (43%) which was obtained as a colorless viscous oil that solidified upon standing. Fragmenting mass analysis supports the stated structure. HRMS *m/z* calcd for $C_{22}H_{24}N_4O_2$ $(M)^+$ 376.1899, found 376.1892.

EXAMPLE 123

2-(*n*-Hexyloxy)-6-(1-piperazinyl)pyrazine.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(*n*-hexyloxy)pyrazine (1.54 g, 7.17 mmol; obtained according to the procedure of example 50, step 1, starting from *n*-hexanol), piperazine (1.90 g, 22.1 mmol) and K_2CO_3 (0.99 g, 7.16 mmol). The yield of the title compound was 1.21 g (64%) which was obtained as a colorless oil. HRMS *m/z* calcd for $C_{14}H_{24}N_4O$ $(M)^+$ 264.1950, found 264.1953. Anal. ($C_{14}H_{24}N_4O$) C, H, N.

EXAMPLE 124

2-(Propargyloxy)-6-(1-piperazinyl)pyrazine, Maleate.

The title compound was prepared according to the procedure of example 50, step 2, starting from 2-chloro-6-(propargyloxy)pyrazine (1.70 g, 10.1 mmol; obtained according to the procedure of example 50, step 1, starting from propargyl alcohol), piperazine (1.91 g, 22.2 mmol) and K_2CO_3 (1.39 g, 10.1 mmol) with the exception that the final filtration through alumina was omitted. Following repeated chromatography on silica, solvents were evaporated off. The yield of the free base of the title compound was 0.48 g (22%) which was obtained as a beige oil. The free base was converted into its maleate salt. HRMS *m/z* calcd for $C_{11}H_{14}N_4O$ $(M)^+$ 218.1168, found 218.1158. Anal. ($C_{11}H_{14}N_4O \cdot C_4H_4O_4$) C, H, N.

PREPARATION OF PHARMACEUTICAL COMPOSITIONS

EXAMPLE: Preparation of tablets

	Ingredients	mg/tablet
1.	Active compound	10.0
2.	Cellulose, microcrystalline	57.0
3.	Calcium hydrogen phosphate	15.0
4.	Sodium starch glycolate	5.0
5.	Silicon dioxide, colloidal	0.25
6.	Magnesium stearate	0.75

The active ingredient 1 is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, and the resultant mixture is mixed for about 5 minutes and compressed into tablet form with or without film-coating.

Pharmacological tests

The ability of a compound of the invention to bind or act at specific 5-HT receptor subtypes can be determined using *in vitro* and *in vivo* assays known in the art. The biological activity of compounds prepared in the Examples was tested using different tests.

Affinity assay

The 5-HT_{2C} receptor affinity of compounds in the Examples was determined in competition experiments, where the ability of each compound in serial dilution to displace ^{3}H-labelled 5-HT, bound to membranes prepared from a transfected HEK293 cell line stably expressing the human 5-HT_{2C} receptor protein, was monitored by Scintillation Proximity Assay technology. Non-specific binding was defined using 5 μM mianserin. Results obtained for exemplary compounds of the invention are illustrated in Table 1 below. Typically, the 5-HT_{2C} receptor affinity values (K_i, nM) were in the range of 1 nM to 1500 nM.

Table 1. 5-HT_{2C} receptor Affinity

Compound	K_i (nM)
Example 2	8
Example 12	197
Example 15	616
Example 18	92
Example 20	28
Example 23	478
Example 32	48
Example 48	37

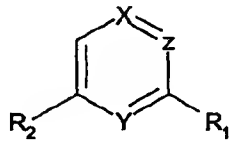
Efficacy assay

The agonist efficacy at the 5-HT_{2c} receptor of the compounds in the Examples was determined by the ability of each compound to mobilise intracellular calcium in transfected HEK293 cells, stably expressing the human 5-HT_{2c} receptor protein, using the calcium-chelating fluorescent dye FLUO-3 (Sigma, St. Louis, MO, U.S.A.).

Typically, the maximum responses of 5-HT_{2c} agonists were in the range of 20-100% relative to the maximum response of 5-HT (serotonin) at a concentration of 1 μM.

CLAIMS

1. A compound of the general formula (I):



(I)

wherein

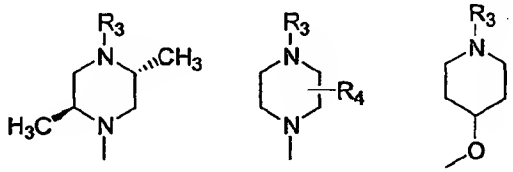
(i) X and Y represent both nitrogen and Z represents CH, forming a pyrazine derivative, or

(ii) X and Z represent both CH and Y represents nitrogen, forming a pyridine derivative, or

(iii) X represents C-CF_3, Z represents CH, and Y represents nitrogen, forming a 4-trifluoromethylpyridine derivative, or

(iv) Y and Z represent both nitrogen and X represents CH, forming a pyrimidine derivative, and

wherein R_1 and R_2 are each, independently, selected from a group A consisting of



or from a group B, consisting of aryl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkoxy, aryloxy-C_2-C_6-alkoxy, heteroaryloxy-C_2-C_6-alkoxy, 1-indanyloxy, 2-indanyloxy, aryloxy, heteroaryloxy, arylthio, heteroarylthio, C_5-C_6-cycloalkylthio, C_5-C_8-alkoxy, C_5-C_8-alkylthio, C_3-C_6-alkynyloxy, C_3-C_6-alkenyloxy, fluoro-C_2-C_4-alkoxy, C_4-C_8-cycloalkyloxy, C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, halogen, aryl-C_1-C_4-alkylthio, heteroaryl-C_1-C_4-alkylthio, aryl-C_1-C_4-alkylamino, heteroaryl-C_1-C_4-alkylamino, hetcroaryl and aryl;

with the proviso that:

(i) R_1 and R_2 are different and are not both selected from group A or group B at the

same time;

(ii) when formula (I) is a pyrazine derivative R_1 or R_2 are other than phenylthio, phenylmethylthio, phenyl or phenyl substituted by halogen;

(iii) R_1 in formula (I) is halogen, only when (I) is a pyrazine derivative and when R_2 simultaneously is 2-methylpiperazin-1-yl, 2-ethylpiperazin-1-yl, or *trans*-2,5-dimethylpiperazin-1-yl;

(iv) when formula (I) is a pyrazine derivative and R_1 is 4-piperidinyloxy, R_2 is other than 3-pyridinylmethoxy, 4-quinolinylmethoxy and 3-(4-pyridinyl)propoxy;

(v) when both X and Z are CH and Y is N in formula (I), forming a pyridine derivative, and R_1 is 1-piperazinyl or 4-methylpiperazin-1-yl, then R_2 is other than 2-phenylethyl, benzyloxy, benzylamino, phenylthio, phenoxy, substituted phenoxy, C_4-C_8-cycloalkyloxy and C_3-C_8-cycloalkylmethoxy;

(vi) when X is CH and Z and Y both are nitrogen in formula (I), forming a pyrimidine derivative, and R_2 is 1-piperazinyl, then R_1 is other than phenoxy, phenyl or phenyl substituted by bromo, and C_5-C_8 alkoxy; and when R_2 is 4-methylpiperazin-1-yl or 4-(2-hydroxyethyl)piperazin-1-yl, then R_1 is other than 5-nitro-2-furyl;

(vii) when X is CH and Z and Y both are nitrogen in formula (I), forming a pyrimidine derivative, and R_1 is 1-piperazinyl, then R_2 is other than C_5-C_8 alkoxy;

and where R_3 is H or C_{1-4}-alkyl, allyl, 2-hydroxyethyl, 2-cyanoethyl, or a nitrogen protecting group, or a prodrug moiety such as an acyl- or an alkoxycarbonyl group forming a cleavable amide or carbamate linkage;

R_4 is hydrogen, or C_{1-4} alkyl;

and wherein any aryl or heteroaryl residue, alone or as part of another group, in R_1 or R_2 may be independently substituted in one or more positions, by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{2-4}-acyl, C_{1-4}-alkylsulphonyl, cyano, nitro, hydroxy, C_{2-6}-alkenyl, C_{2-6}-alkynyl, fluoromethyl, trifluoromethyl, trifluoromethoxy, halogen, $-N(R_5)(R_6)$, aryl, aryloxy, arylthio, aryl-C_{1-4}-alkyl, aryl-C_{2-4}-alkenyl, aryl-C_{2-4}-alkynyl, heteroaryl, heteroaryloxy, heteroarylthio or heteroaryl-C_{1-4}-alkyl, aryl-C_{1-4}-alkoxy, aryloxy-C_{1-4}-alkyl, dimethylamino-C_{2-4}-alkoxy; and

wherein any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in R_1 or R_2 in turn may be substituted in one or more postions, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, trifluoromethyl, cyano, hydroxy or dimethylamino; and

R_5 and R_6 independently of each other are hydrogen, methyl or ethyl, or together with the nitrogen atom to which they are bound form a pyrrolidine, piperazine, morpholine, thiomorpholine or a piperidine ring;

and pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof.

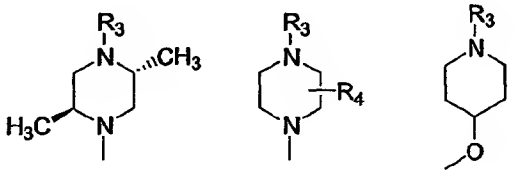
2. The compound according to claim 1 wherein X and Y represent both nitrogen and Z represents CH, forming a pyrazine derivative.

3. The compound according to claim 1, wherein X and Z represent both CH and Y represents nitrogen, forming a pyridine derivative.

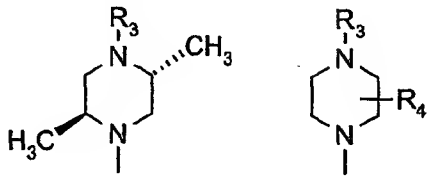
4. The compound according to claim 1, wherein formula (I) represents a 4-trifluoromethylpyridine derivative.

5. The compound according to claim 1 wherein Y and Z represent both nitrogen and X represents CH, forming a pyrimidine derivative.

6. The compound according to claim 1 wherein R_3 is hydrogen and R_1 or R_2 is selected from

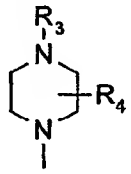


7. The compound according to claim 1 wherein R_1 or R_2 is selected from



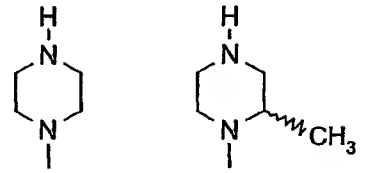
and where R_3 is hydrogen and R_4 is selected from hydrogen, methyl or ethyl.

8. The compound according to claim 1 wherein R_1 or R_2 is

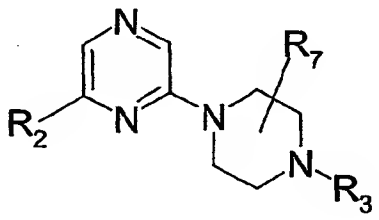


and where R_3 is hydrogen and R_4 is selected from hydrogen, methyl or ethyl.

9. The compound according to claim 1, wherein R_1 or R_2 is selected from



10. The compound according to claim 1 with the general formula (II):



(II)

wherein

R_2 and R_3 are as defined above;

R_7 is hydrogen or C_{1-4}-alkyl;

and any aryl and heteroaryl residue, alone or as part of another group, in R_2 may be substituted in one or more positions, preferably one or two, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{2-4}-acyl, C_{1-4}-alkylsulphonyl, cyano, nitro, hydroxy, C_{2-6}-alkenyl, C_{2-6}-alkynyl, fluoromethyl, trifluoromethyl, trifluoromethoxy, halogen, -N(R_5)(R_6), aryl, aryloxy, arylthio, aryl-C_{1-4}-alkyl, aryl-C_{2-4}-alkenyl, aryl-C_{2-4}-alkynyl, heteroaryl, heteroaryloxy, heteroarylthio or heteroaryl-C_{1-4}-alkyl, aryl-C_{1-4}-alkoxy, aryloxy-C_{1-4}-alkyl, dimethylamino-C_{2-4}-alkoxy; and

any aryl or heteroaryl residue as substituents on aryl or heteroaryl, alone or as part of another group, in R_2 in turn may be substituted in one or more postions, preferably one, independently of each other by C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, trifluoromethyl, cyano, hydroxy or dimethylamino;

R_5 and R_6 are as defined above.

11. The compound according to claim 10 wherein R_3 is hydrogen.

12. The compound according to claim 10 wherein R_7 is selected from hydrogen, methyl or ethyl.

13. The compound according to claim 10 wherein R_7 is methyl and where said methyl is attached to the C2-position of the piperazine ring.

14. The compound according to claim 10 wherein R_7 is hydrogen.

15. The compound according to claim 1, which is selected from the group consisting of:

2-(Benzyloxy)-6-(1-piperazinyl)pyrazine,
2-[(2-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(3-Methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(3,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-(1-Naphthylmethoxy)-6-(1-piperazinyl)pyrazine,

2-(1-Phenylethoxy)-6-(1-piperazinyl)pyrazine,
2-[1-(3-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[1-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-(3,4-Dihydro-2*H*-chromen-4-yloxy)-6-(1-piperazinyl)pyrazine,
2-(2-Phenylethoxy)-6-(1-piperazinyl)pyrazine,
2-[(2-Phenoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[2-(3-Chlorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(2-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(3-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(4-Methoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(2,5-Dimethoxyphenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[(2-Phenylethyl)sulfanyl]-6-(1-piperazinyl)pyrazine,
2-[(5-Fluoro-2-methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(3-Cyanobenzyl)oxy]-6-(1-piperazinyl)pyrazine,
2-[(2-Chlorobenzyl)sulfanyl]-6-(1-piperazinyl)pyrazine,
2-[2-(4-Dimethylaminophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(1*H*-Indol-3-yl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(1*H*-Indol-1-yl)ethoxy]-6-(1-piperazinyl)pyrazine,
4-(Benzyloxy)-2-(1-piperazinyl)pyrimidine,
4-[(2-Methoxybenzyl)oxy]-2-(1-piperazinyl)pyrimidine,
2-{[3-(Benzyloxy)benzyl]oxy}-4-(1-piperazinyl)pyrimidine,
2-Benzyl-6-(1-piperazinyl)pyrazine,
2-[(3,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine,
1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine,
1-[6-(Benzyloxy)-2-pyrazinyl]-2-ethylpiperazine
1-[6-(Benzyloxy)-2-pyrazinyl]-*trans*-2,5-dimethylpiperazine.
2-[2-(2-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine,
2-(2,3-Dihydro-1*H*-inden-1-ylmethoxy)-6-(1-piperazinyl)pyrazine
2-(4-Phenoxybutoxy)-6-(1-piperazinyl)pyrazine.
2-[(5-Phenoxypentyl)oxy]-6-(1-piperazinyl)pyrazine.
2-[(2,5-Dimethoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine.
2-{[2-(2-Phenylethyl)benzyl]oxy}-6-(1-piperazinyl)pyrazine
(2*R*)-1-[6-(Benzyloxy)-2-pyrazinyl]-2-methylpiperazine,

2-[2-(2,6-Difluorophenoxy)ethoxy]-6-(1-piperazinyl)pyrazine
2-[2-(2-Naphthyloxy)ethoxy]-6-(1-piperazinyl)pyrazine
2-(1-Methyl-2-phenylethoxy)-6-(1-piperazinyl)pyrazine
2-{[2-(Phenoxymethyl)benzyl]oxy}-6-(1-piperazinyl)pyrazine
2-[(5-Fluoro-2-methoxybenzyl)oxy]-6-(1-piperazinyl)pyrazine
2-[(2,5-Difluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine
2-[(2-Fluorobenzyl)oxy]-6-(1-piperazinyl)pyrazine
2-(Benzo[*b*]thiophen-3-ylmethoxy)-6-(1-piperazinyl)pyrazine,
2-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-6-(1-piperazinyl)pyrazine,
2-[1-(2,6-Difluoro-phenyl)-ethoxy]-6-(1-piperazinyl)pyrazine,
2-(2-Naphthalen-2-yl-ethoxy)-6-(1-piperazinyl)pyrazine,
2-[3-(Naphthalen-2-yloxy)-propoxy]-6-(1-piperazinyl)pyrazine,
2-[2-(7-Methoxy-naphthalen-2-yloxy)-ethoxy]-6-(1-piperazinyl)pyrazine,
2-[5-(4-Chlorophenyl)-2-methylfuran-3-ylmethoxy]-6-(1-piperazinyl)pyrazine,
2-(1*H*-Indol-4-ylmethoxy)-6-(1-piperazinyl)pyrazine,
and their pharmacologically acceptable salts and solvates.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 as an active ingredient, together with a pharmaceutically acceptable carrier.

17. A method for the prophylaxis or treatment of a serotonin-related medical condition, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 15.

18. The method according to claim 17, wherein the medical condition is related to the 5-HT_{2c} receptor.

19. The method according to claim 17 wherein the medical condition is an eating disorder.

20. The method according to claim 17, wherein the medical condition is obesity.

21. The method according to claim 17, wherein the medical condition a memory disorder.

22. The method according to claim 17, wherein the medical condition is a mood disorder.

23. The method according to claim 17, wherein the medical condition is an anxiety disorder.

24. The method according to claim 17, wherein the medical condition is selected from sexual dysfunctions, epilepsy and urinary disorders.

25. The method according to claim 17, wherein the medical condition is pain.

26. The method according to claim 17, wherein the medical condition is substance abuse.

27. The method according to claim 17, wherein the medical condition is schizophrenia.

28. Use of a compound according to any one of claims 1 to 15 in the manufacture of a medicament for the prophylaxis or treatment of a serotonin-related medical condition.

29. The use according to claim 28, wherein the medical condition is related to the 5-HT_{2c} receptor.

30. The use according to claim 28 wherein the medical condition is an eating disorder.

31. The use according to claim 28, wherein the medical condition is obesity.

32. The use according to claim 28, wherein the medical condition a memory disorder.

33. The use according to claim 28, wherein the medical condition is a mood disorder.

34. The use according to claim 28, wherein the medical condition is an anxiety disorder.

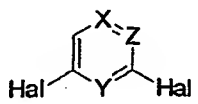
35. The use according to claim 28, wherein the medical condition is selected from sexual dysfunctions, epilepsy and urinary disorders.

36. The use according to claim 28, wherein the medical condition is pain.

37. The use according to claim 28, wherein the medical condition is substance abuse.

38. The use according to claim 28, wherein the medical condition is schizophrenia.

39. A method of making a compound of claim 1, taking a compound of the following formula:



wherein

(i) X and Y represent both nitrogen and Z represents CH, forming a pyrazine derivative, or

(ii) X and Z represent both CH and Y represents nitrogen, forming a pyridine derivative, or

(iii) X represents C-CF_3, Z represents CH, and Y represents nitrogen, forming a 4-trifluoromethylpyridine derivative, or

(iv) Y and Z represent both nitrogen and X represents CH, forming a pyrimidine derivative, and wherein

each Hal is independently a halogen;

and reacting the compound with one or more chemical reagents in one or more steps to produce a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/02569

A. CLASSIFICATION OF SUBJECT MATTER
C07D 241/18, 241/20, 405/12, 213/82, 213/60, 213/64, 213/74, A61K 031/497, 31/445, 31/4427, A61P 25/00, A61P 25/18, A61P 13/00, A61P 25/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 39, 1996, Malgorzata Dukat et al: "Structure-Activity Relationships for the Binding of Arylpiperazineses and Arylbiguanides at 5-HT3 Serotonin Receptors, page 4017 - page 4026, RN 181650-31-7, CAPLUS-STN, Compound 3-tabel 1	1-37
X	EP 0462638 A1 (AKZO N.V.), 27 December 1991 (27.12.91), CAPLUS-STN, RN 139722-61-5, 139722-62-6, 139722-75-1	1-37
X	EP 1023898 A1 (ADIR ET COMPAGNIE), 2 August 2000 (02.08.00), CAPLUS-STN, RN 118708-88-6, 286410-54-6, Reactant	1-37

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2002	22-02-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer FERNANOD FARIETA/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/02569

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0345808 A1 (BRISTOL-MYERS COMPANY), 13 December 1989 (13.12.89), CAPLUS-STN, RN 127561-42-6, 127561-45-9, pages 39-45	1-37
A	WO 9911619 A1 (MERCK SHARP & DOHME LIMITED), 11 March 1999 (11.03.99), CAPLUS-STN, RN 221282-09-3	1-37
A	WO 9411363 A1 (ASAHI KASEI KOGYO KABUSHIKI KAISHA), 26 May 1994 (26.05.94), CAPLUS-STN, RN 118708-88-6, 163613-49-8, 163613-50-1	1-37
A	J. Heterocyclic Chem., Volume 34, 1997, Gregory M. Shutske et al: "Synthesis of Some Piperazinylpyrazolo(3,4-b)pyridines as Selective Serotonin Re-uptake Inhibitors", page 789 - page 795, CAPLUS-STN, RN 193481-65-1	1-37
A	Neuroscience & Biobehuvioral Reviews, Volume 15, 1991, R.J. Rodgers et al: "Differential Effects of Novel Ligands for 5-HT Receptor Subtypes on Nonopioid Defensive Analgesia in Male Mice", page 489 - page 495, RN 109028-10-6, 124756-23-6, 64022-27-1, 85273-95-6, 87051-43-2, CAPLUS-STN	1-37
A	Psychopharmacology, Volume 99, 1989, Herbert Y. Meltzer: "Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia", page 18 - page 27	1-37
A	Biol Psychiatry, Volume 31, 1992, Hong Shick Lee et al: "Effect of the Serotonin Agonist, MK-212, on Body Temperature in Schizophrenia", page 460 - page 470	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/02569

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Journal of Medicinal Chemistry, Volume 21, No. 6 1978, William C. Lumma, Jr. et al: "Piperazinylpyrazines with Central Serotoninmimetic Activity, page 536 - page 542, compound --	1-37
A	Patent Abstract of Japan, abstract of JP 7-300474 A (ASAHI CHEM IND CO LTD), 14 November 1995 (14.11.95), abstract --	1-37
A	WO 0050401 A1 (F. HOFFMAN-LA ROCHE AG), 31 August 2000 (31.08.00), CAPLUS-STN, RN 290300-93-5, 290300-95-7 --	1-37
A	WO 9842712 A1 (SYNTHELABO), 1 October 1998 (01.10.98), CAPLUS-STN, RN 214045-90-6 --	1-37
A	WO 0017163 A1 (YAMANOUCHI PHARMACEUTICAL CO., LTD.), 30 March 2000 (30.03.00), Formel 1 --	1-37
A	Neuroscientist, Volume 6, No. 4, 2000, Bryan L. Roth et al: "The Multiplicity of Serotonin Receptors: Uselessly Diverse Molecules or an Embarrassment of Riches", page 252 - page262, table 1 -- --------	1-37

INTERNATIONAL SEARCH REPORT

International application No.
SE01/02569

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-27
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/SE 01/02569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0462638 A1	27/12/91	AU 642369 B	14/10/93
		AU 7825291 A	12/12/91
		CA 2043604 A	12/12/91
		FI 912759 A	12/12/91
		IE 911774 A	18/12/91
		JP 5140108 A	08/06/93
		NZ 238438 A	25/09/92
		PT 97903 A	31/03/92
		US 5135931 A	04/08/92
		ZA 9104204 A	25/03/92
EP 1023898 A1	02/08/00	AU 1355300 A	27/07/00
		AU 3041899 A	01/11/99
		BR 0000158 A	19/09/00
		CN 1266057 A	13/09/00
		EP 1067841 A	17/01/01
		FR 2788772 A,B	28/07/00
		HU 0000308 D	00/00/00
		JP 2000212162 A	02/08/00
		NO 20000373 A	27/07/00
		PL 338027 A	31/07/00
		US 6239129 B	29/05/01
		ZA 200000336 A	15/08/00
EP 0345808 A1	13/12/89	SE 0345808 T3	
		AT 116982 T	15/01/95
		AU 624147 B	04/06/92
		AU 3628289 A	14/12/89
		CA 1337421 A	24/10/95
		CY 1846 A	08/03/96
		DE 68920482 D,T	01/06/95
		DK 283589 A	11/12/89
		ES 2067500 T	01/04/95
		FI 95698 B,C	30/11/95
		FI 892787 A	11/12/89
		HK 83295 A	01/06/95
		IE 66569 B,L	24/01/96
		JP 2085277 A	26/03/90
		JP 2786480 B	13/08/98
		KR 128210 B	02/04/98
		NO 174296 B,C	03/01/94
		NO 892381 D	00/00/00
		PT 90805 A,B	29/12/89
		SG 9590746 A	01/09/95
		US 4954502 A	04/09/90
		ZA 8904377 A	26/02/92
WO 9911619 A1	11/03/99	AU 8876698 A	22/03/99
		GB 9718833 D	00/00/00
WO 9411363 A1	26/05/94	EP 0668276 A	23/08/95
		JP 6199815 A	19/07/94
		US 5578596 A	26/11/96

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/SE 01/02569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0050401 A1	31/08/00	AU 3154900 A	14/09/00
		EP 1157005 A	28/11/01
		NO 20014098 A	23/08/01
		US 6225316 B	01/05/01
WO 9842712 A1	01/10/98	AU 6923998 A	20/10/98
		EP 0971928 A	19/01/00
		FR 2761071 A,B	25/09/98
		ZA 9802362 A	23/09/98
WO 0017163 A1	30/03/00	AU 5654499 A	10/04/00
		BR 9914018 A	03/07/01
		CN 1319091 T	24/10/01
		EP 1122242 A	08/08/01